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Vaseretic is contraindicated in patients who are hypersensitive to any component of this product or to other sulfonamide-derived drugs and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.
Dosage must be individualized; the fixed combination is not for initial therapy.
Evaluation of the hypertensive patient should always include assessment of renal function.
For a Brief Summary of Prescribing Information, see adjacent pages.

USE IN PREGNANCY: **When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus.** When pregnancy is detected, Vaseretic (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

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TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General; Enalapril Maleate; Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions*, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy: Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*, below.)

Enalapril Maleate; Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats, and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide; Teratogenic Effects. Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General; Enalapril Maleate; Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions.*)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients; Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions; Enalapril Maleate; Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium. Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide; When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs— In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution

10 mg

25 mg

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assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse bone marrow assay.
Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.
Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.
Pregnancy, Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*
Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*
Clinical Laboratory Test Findings: Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.
Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia, atrial fibrillation; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*

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(Ostwald PF, Baron BC, Byl NM, Wilson FR: Performing arts medicine. West J Med 1994; 160:48-52)

Arts medicine has come of age, resulting from 3 important developments over the past decade: improved methods of diagnosis and treatment, an awareness that artists suffer from special problems related to their occupation and lifestyle, and the establishment of health programs emphasizing an interdisciplinary approach to these patients. We focus on the patterns of illness afflicting performing artists, specifically dancers, singers, actors, and instrumental musicians, and explain some of the things a health care team can do in treating these patients. The conditions governing these patients' lives—early exposure to high expectations of excellence, incessant demands for perfection, long periods of intense practicing, fierce competition, high levels of anxiety associated with performance, and uncertain careers—need to be understood. Levels of disease and disability are remarkably high, but artists often ignore symptoms. We discuss the musculoskeletal, neurologic, vocal, psychological, and other syndromes found among performers and some of the difficulties in treating them. The prevention of injury, conservative management, collaboration with teachers, and a psychotherapeutic approach are desirable. Arts medicine programs for professional consultation exist in several major cities of the United States and abroad. Although research is needed regarding the effectiveness of health care services for performing artists, the scientific literature devoted to this field is growing.

PERFORMING ARTS MEDICINE
DANCERS' INJURIES
SINGERS' THROAT INFECTIONS
MUSICIANS' DISORDERS

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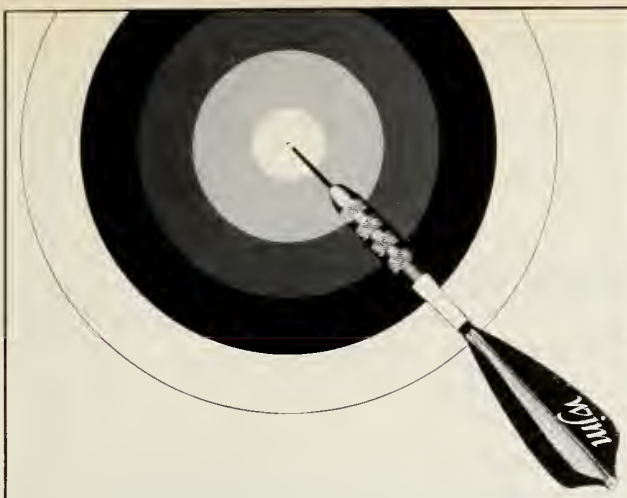

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1. A. Morales et al., New England Journal of Medicine 1221. November 12, 1981
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
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PROGRAM PROFILE

Center For Musculoskeletal Tumors

Malignant tumors of the musculoskeletal system, whether bone or soft tissue tumors, are extremely rare: only an estimated 4,000 new cases of osteogenic sarcoma, and 6,000 new cases of soft tissue sarcomas of the extremities, are diagnosed each year. Consequently, orthopaedic surgeons in private practice may see a malignant bone tumor perhaps once every 10 years.

A CASE STUDY

A 35-year-old law student developed progressive pain in his hip. He eventually fell, sustaining a fracture through his femoral neck. At that time, a big tumor was detected in the proximal third of this femur, with the added complication of spillage into the hip joint. A biopsy confirmed an osteosarcoma, with no evidence of metastatic tumor. After three courses of chemotherapy, the patient underwent surgery.

This was a complicated case because of the tumor spillage. In order to achieve an adequate margin around the tumor, Dr. Menendez not only had to remove the proximal femur and surrounding musculature, but also the entire hip joint en bloc, including acetabulum, as well. Because the patient asked the team to reconstruct a leg that he could walk on and a hip he could move, surgeons opted against a fusion and instead performed a procedure that involved an allograft to reconstruct the acetabulum, and a custom endoprosthesis to replace the joint.

Following surgery, the patient underwent some follow-up chemotherapy. He had essentially 100 percent tumor necrosis, and an excellent response to chemotherapy. His allografts and junctions have since healed, and after a year he is ambulating with a cane — and continuing his pursuit of a law degree.

In sharp contrast, Lawrence R. Menendez, M.D., associate professor of Orthopaedic Surgery at the University of Southern California School of Medicine and director of Orthopaedic Oncology at USC University Hospital, performs more than 200 procedures a year. This volume, supported by a multidisciplinary team of medical oncologists, musculoskeletal pathologists, vascular and plastic surgeons and radiation therapists, along with nursing, social and rehabilitative services at USC University Hospital, has allowed Dr. Menendez to develop and maintain an expertise in this specialized field.

USC University Hospital

USC UNIVERSITY HOSPITAL
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Bone Tumors

Benign and malignant bone tumors each present its own specific treatment challenges, making it imperative that an accurate diagnosis be established. Dr. Menendez treats the most common malignant bone tumor, osteogenic sarcoma, with biopsy and then he develops a comprehensive treatment strategy that may include staging studies, pre- and post-operative treatment with chemotherapy and/or radiation therapy, surgery and reconstruction, rehabilitation, and long-term follow-up to detect tumor recurrence. Reconstruction options include allografts, autologous bone grafts, prosthetic implants or a combination of these materials.

Soft Tissue Tumors

Soft tissue tumors that appear benign may actually be malignant, again requiring absolute accuracy of diagnosis. Oftentimes, large soft tissue resections will require extensive reconstructive surgery involving vascularized flaps to provide tissue coverage. At USC, Dr. Menendez has immediate access to the expertise of vascular surgeons, general surgeons and reconstructive surgeons to provide necessary treatment. As a result, he is prepared for any situation.

Close Contact With Referring Physicians

Follow-up is a vital aspect of the program. Dr. Menendez examines X-rays and exchanges notes with referring physicians, keeping all parties involved. He sends referring physicians a letter every time he sees their patients in follow-up, whether it is a month or five years later. Dr. Menendez follows patients who had malignancies every three months for the first two years, and then every six months. Regular check-ups are recommended for the life of the patient, although Dr. Menendez considers the patient cured if five years pass without a recurrence of metastatic disease.

Lawrence R. Menendez, M.D.:
At the forefront of orthopaedic oncology

About the Director

Lawrence R. Menendez, M.D., predicts that the future of musculoskeletal oncology will be centered within the major academic centers across the country, and believes USC is well-positioned to offer leadership in this complex field.

Born and raised in New Jersey, Dr. Menendez attended Middlebury College in Vermont, where he received his bachelor's degree in biology. He earned his medical degree from the New York University School of Medicine, completed a general surgery internship at Columbia Presbyterian Medical Center, and returned to New York University for his orthopaedic surgery residency. He also did an oncology fellowship at the University of Florida with William F. Enneking, M.D., one of the founders of orthopaedic oncology as a specialty.

From 1985 to 1989, Dr. Menendez served on the full-time USC faculty as assistant professor of Orthopaedic Surgery, and then became a part-time faculty member, moving his private practice to The Hospital of the Good Samaritan in Los Angeles. During this time, he continued to run the orthopaedic oncology service at Los Angeles County + USC Medical Center. In July 1992, he was recruited back to USC full time as associate professor.

School of Medicine

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Dr Vincent is in private practice in Pasadena, California.

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★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

California Medical Association's Western Scientific Assembly and 123rd Annual Session

March 17-23, 1994

Disneyland Hotel, Anaheim

This FREE PROGRAM is open to all Annual Session Badge Holders

GOLDEN APPLE AWARD AND RECEPTION

"Doctor James Lind: Taking the History and Changing the History of the World"

Friday, March 18, 5:30 pm
Disneyland Hotel Convention Complex

Doctor Sherman M. Mellinkoff has been selected by the Committee on Scientific Assemblies to receive CMA's 1994 Golden Apple Award. This award spotlights exceptional physicians who have made a lifelong commitment to teaching and are renowned for their charismatic, scientific and educational talents.

Doctor Mellinkoff is Emeritus Professor of Medicine at the UCLA School of Medicine, where he served as Dean for 24 years. Following his medical education (Alpha Omega Alpha) and internship at Stanford in the mid-1940s, he served in the Army Medical Corps for two years and subsequently as Assistant, Associate and Chief Resident on the Osler Service at Johns Hopkins Hospital in Baltimore, and as Fellow in Gastroenterology at the University of Pennsylvania. In 1981 he received the Abraham Flexner Award of the Association of American Medical Colleges for his outstanding contributions to medical education.

Doctor Mellinkoff's address will explore the work of 18th century physician, James Lind, whose clinical skill changed the course of medical and world history. Between 1500 and 1800 more seamen were killed by scurvy than by all other causes. Citrus juice, Lind discovered, was a cure for scurvy, and a practical means of preventing it on long voyages. Rid of this debilitating disease, the British Navy defeated Napoleon's fleet at the Battle of Trafalgar! Correct diagnosis and treatment still rely on taking an accurate medical history. Doctor Mellinkoff will discuss the applicability of Lind's methods to modern clinical practice.

We encourage all to attend CMA's Golden Apple Award presentation and reception to help us honor this outstanding teacher.

The financial assistance of Cooperative of American Physicians, Inc. - Mutual Protection Trust is gratefully acknowledged in making this reception possible.

The Western Scientific Assembly Courses: March 17-20, 1994

CMA's 1994 Western Scientific Assembly offers an exceptional educational opportunity that meets *your needs* for clinical courses, workshops and seminars that are:

- Highest quality
- Convenient
- Practical
- Economical
- Multispecialty
- CME Approved

Primary care physicians and specialists must daily assess, evaluate, and treat patients who present with complex symptoms requiring knowledge that spans a broad range of specialties. The 1994 Western Scientific Assembly provides the most time-efficient, and cost-effective opportunity to learn the latest clinical and research developments at the largest multispecialty meeting on the West Coast!

Dozens of available courses are designed to provide you with useful, practical clinical knowledge and skills immediately applicable to your day-to-day practice needs. Courses average 3-4 hours of Category I CME credit and have also been approved for American Academy of Family Physicians prescribed credit and American College of Emergency Physicians Category I credit.

THURSDAY COURSES March 17

AM 01 Basic Cardiac Life Support

PM 02 What's Up Doc? Cartoons that Sell a Smokefree Lifestyle

03 Reducing Your Overhead and Realizing Increased Income

FRIDAY COURSES March 18

AM 04 Advanced Cardiac Life Support: Provider Course (2-day course meets Friday and Saturday)

05 Practical Neurology

06 Cost-Effective Pulmonary Medicine

07 Skin Cancer: A Clinical and Histopathologic Update

08 Pediatric Otolaryngology: What Gatekeepesr Need to Know

09 How to Improve Your Collection Results

10 GRATEFUL MED Training: Referencing the NLM Databases

PM 11 Common Neurosurgical Problems in Medical Practice

12 Emergencies in Primary Care

13 Current Issues in Dermatology

14 Cancer Detection & Follow-Up in Primary Care

15 They Can't Take That Away From Me: Medicine in Transition

SATURDAY COURSES March 19

16 Advanced Cardiac Life Support: Provider Retraining

17 Pediatric Emergencies

18 Dilemmas In Women's Imaging

19 Drug & Alcohol Emergencies in Primary Care

20 New Anesthetic Agents in Ambulatory Care

21 Caring for Terminally Ill: Caring When You Can't Cure

22 Resurgence of TB: The New Face of an Old Nemesis

23 Immunologic Controversies In Private Practice

24 GRATEFUL MED Training: Referencing the NLM Databases

PM 25 Health Care Issues for Women Over 40

26 Psychiatric Emergencies in Primary Care

27 Frontiers in Nuclear Oncology

28 Practical Aspects of Occupational Medicine

29 Cultural Competence in Medical Practice

30 HIV/AIDS Essential Issues for Private Practice

SUNDAY COURSES March 20

AM 31 Urology for Primary Care Physicians

32 Multiple Views of Pain Management

33 Long Term Care Update

34 Outpatient Procedures for the Primary Care Physician

35 Future Trends in Outpatient Surgery

36 Ophthalmologist-Gatekeeper: Managed Eye Care

37 Suture Course

38 Legal Clinic on Combatting Fraud and Abuse

PM 39 Musculoskeletal Trauma in Children and Adolescents

40 Risk In Cost-Contained Care

41 No-Scalpel Vasectomy Orientation and Workshop

42 Silicone Breast Implants: Fact vs. Fiction

43 Residency Selection and Career Planning

To receive a copy of the 40-page Advance Program which provides complete objectives schedules, CME information, and registration details, please call (415) 882-3384.

This FREE PROGRAM is open to all Annual Session Badge Holders

DISTINGUISHED SPEAKER

Robert E. Rakel, MD

Sunday, March 20, 1994, 1:00 - 2:00 pm
Disneyland Hotel
Convention Complex Marina Ballroom

THE FUTURE OF GENERAL MEDICINE

Doctor Robert E. Rakel, host of "Family Practice Update" presented every Sunday on Lifetime Television, will discuss the current state of healthcare reform in the United States and the impact it will have on all physicians, especially those in primary care. Can the specialty maldistribution problem be corrected and can quality healthcare be maintained while healthcare reform focuses on lower cost? Doctor Rakel will look at the current options being proposed and offer comments on those most likely to make it through Congress.

Doctor Rakel received his MD at the University of Cincinnati, College of Medicine in 1958. Following residency training, he began his career in private practice in Newport Beach, California. Currently, Doctor Rakel serves as the Richard M. Kleberg, Sr. Professor and Chair of the Department of Family Medicine, as well as the Associate Dean for Academic And Clinical Affairs at Baylor College of Medicine in Houston, Texas. He was previously Chair of the Department of Family Medicine at the University of Iowa and the University of California, Irvine, as well as Director of the Family Practice Residency Program at Hoag Memorial Hospital in Newport Beach.

In addition, Doctor Rakel has edited several important textbooks including Textbook of Family Practice, Conn's Current Therapy, Essentials of Family Practice, and Yearbook of Family Practice. He serves on the editorial boards of Journal of the American Medical Association, The Journal of Family Practice, and Family Practice News.

We are pleased to welcome Doctor Rakel back to California this year as our Distinguished Speaker and invite all to come listen to his provocative discussion on the future of general medicine.

CMA's Western Scientific Assembly and Annual Session

CMA HOUSE OF DELEGATES

The CMA House of Delegates meets each day, Saturday, March 19 through Wednesday, March 23. House Speaker, Doctor Jack McCleary, notes that the current schedule of the House provides delegates with time to attend scientific programs, view the exhibits and participate in delegation caucuses.

Highlights of this year's House will be the farewell address of outgoing CMA President, David R. Holley, MD, a Monterey radiologist, and the inaugural address of CMA's President-Elect Ralph Ocampo, a San Diego general surgeon.

YOUNG PHYSICIANS SECTION ANNUAL ASSEMBLY

All California physicians under 40 years of age or in their first five years of practice are invited to attend the CMA Young Physicians Section (YPS) Annual Assembly which meets Friday and Saturday, March 18-19. The Assembly debates resolutions on a myriad of medical practice and health policy issues and forwards its recommendations to the CMA House of Delegates, the AMA or its own Executive Committee for action. For additional information, please contact Roger Purdy at (415) 882-5127.

CMA HOSPITAL MEDICAL STAFF SECTION ANNUAL ASSEMBLY

Medical staff leaders from throughout the state will come together at the 1994 CMA-HMSS Annual Assembly. In addition to updates on legal and legislative issues, this year's meeting will feature an educational conference on "Medical Staff Issues: 1994." For more information about the HMSS agenda, registration fees or membership, call (415) 882-5170.

EXHIBIT HALL

During the Western Scientific Assembly, the Exhibit Hall will feature exhibits for everyone: pharmaceuticals, educational displays, computer systems, office systems, insurance, investment opportunities, medical testing systems, health and home products, and much more. Admission is FREE. Be sure to alert your office managers to schedule time to visit the Exhibit Hall.

CMA ALLIANCE

Spouses of physicians can get involved at the Annual Meeting of the CMA Alliance. Board meetings are scheduled from Friday, March 18 through Sunday, March 20. The CMA-A House of Delegates meets Sunday, March 20 through Tuesday, March 22. Educational programs and a silent auction benefiting Community Health Foundation will be held on Friday and Saturday. For more information, call Patty Frisk at (415) 882-5193.

GENERAL INFORMATION

LOCATION

The CMA 1994 Western Scientific Assembly will be held at the Disneyland Hotel, 1150 West Cerritos Avenue, Anaheim, CA 92803. Call (714) 778-6600 for hotel registration information and directions.

All physicians and health professionals attending Western Scientific Assembly courses must pay general registration fees, with the exception of member medical students. Physicians and guests who do not attend any courses are not required to pay a fee. The many FREE programs include: Exhibit Hall, Golden Apple Award and Reception, a Critical Look at the Washington Scene, Distinguished Speaker, Medical Progress: A Miracle at Risk, and others.

PRE-REGISTER BY FEBRUARY 1, 1994 FOR EARLYBIRD SAVINGS

Advance registration closes February 18, after which attendees may register on site at the Disneyland Hotel's Center Lounge:

Thursday, March 17 _____7:00 am to 5:00 pm

Friday, March 18 _____7:00 am to 5:00 pm

Saturday, March 19_____7:00 am to 5:00 pm

Sunday, March20 _____7:00 am to 5:00 pm

FOR MORE INFORMATION

Contact CMA's Western Scientific Assembly office at (415) 882-3384.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 13-14—**First Annual Topics in Critical Care Medicine.** Mayo Clinic-Scottsdale at Ritz Carlton Hotel, Phoenix. Thurs-Fri. Contact: Mayo Clinic-Scottsdale.

January 15-16—**Third Annual Current Topics in Anesthesiology.** Mayo Clinic-Scottsdale at Ritz Carlton Hotel, Phoenix. Sat-Sun. Contact: Mayo Clinic-Scottsdale.

January 21-23—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Scottsdale. Fri-Sun. Contact: Mayo Clinic-Scottsdale.

January 28—**Pediatric Advanced Life Support; Recertification Course.** Phoenix Children's Hospital at Good Samaritan Regional Medical Center. Fri. Contact: (602) 239-3563.

January 28-29—**Pediatrics—25th Anniversary Conference and Celebration.** University of Arizona College of Medicine at Westward Look Resort, Tucson. Fri-Sat. Contact: U of A.

February 2-3—**Pediatric Advanced Life Support; Provider Course.** Phoenix Children's Hospital at YWCA Leadership Center, Phoenix. Wed-Thurs. Contact: (602) 239-3563.

February 13-17—**International Congress VII on Endovascular Interventions on the Cutting Edge.** American College of Angiology. Sun-Thurs. Contact: (602) 266-2200.

February 17-20—**Seventh Annual State-of-the-Art Echocardiography.** American College of Cardiology at Tucson. Thurs-Sun. Contact: (800) 257-4739.

February 19—**Seventh Annual Epilepsy Update.** University of Arizona College of Medicine, Tucson. Sat. Contact: Lynn Mascarella, U of A.

February 21-24—**17th Annual Pediatric Update.** Phoenix Children's Hospital at Marriott's Camelback Inn Resort, Scottsdale. Mon-Thurs. Contact: (602) 239-5784.

February 24-26—**17th Annual Mid-Winter Symposium: Advances in Obstetrics and Gynecology.** American College of Obstetrics and Gynecology. American College of Obstetrics and Gynecology. Thurs-Sat. Contact: (602) 267-5366.

February 24-26—**Mayo Interactive Surgical Symposium.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Mayo Clinic-Scottsdale.

February 24-26—**Epilepsy Update: Basic Mechanisms of Anticonvulsant Treatment.** Healthspan at the Buttes Conference Resort, Phoenix. Thurs-Sat. Contact: (612) 574-7673.

June 2-4—**Arizona Medical Association Annual Meeting**. Scottsdale Plaza Resort. Thurs-Sat. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd. Phoenix, AZ 85013. (602) 246-8901.
Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.
U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

January 23-27—**Western Society of Allergy and Immunology: 32nd Annual Scientific Session.** Western Society of Allergy and Immunology at Ritz-Carlton, Mauna Lani, Island of Hawaii. Sun-Thurs. Contact: Rebecca Smith, PO Box 82268, Portland, OR 97282. (503) 774-3105.

February 3-5—**Immunology and the Clinical Practice of Allergy.** UCSD at San Diego. Thurs-Sat. 20 hrs. $285. Contact: UCSD.

February 18—**Environmental and Occupational Airways Disease: Clinical, Legal and Therapeutic Aspects.** Huntington Memorial Hospital at Braun Auditorium. Fri. Contact: Vivian Mishalany, Asthma and Allergy Center, (818) 397-3383.

March 19—**Immunologic Controversies Facing the Private Practitioner.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott. (415) 882-3384.

ANESTHESIOLOGY

January 16-22—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui, Kaanapali Beach. Sun-Sat. 21 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

January 28-30—**32nd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 23-27—**The Practicing Physician's Approach to the Difficult Headache Patient.** Dannemiller Memorial Educational Foundation at Marriott's Rancho Las Palmas Resort and Country Club, Rancho Mirage. Wed-Sun. Contact: Seymour Diamond, 5252 N Western Ave, Chicago, IL 60625. (312) 907-6226.

March 19-20—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort. Sat-Sun. 9 hrs. $185. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

April 2-3—**22nd Obstetric/Anesthesia Conference.** Ohio State Department of Anesthesiology at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Sun. 20 hrs. $610. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

April 5-8—**Hawaiian Pain Conference.** Ohio State University Department of Anesthesiology at Grand Hyatt, Wailea, Maui. Tues-Fri. 16 hrs. $610. Contact: Arlene Rogers, Ohio State University, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8153.

April 9-10—**39th PGA Conference.** Los Angeles County Society of Anesthesiologists at UCLA Faculty Center. Sat-Sun. 13 hrs. Contact: LACSA, PO Box 90999, Long Beach 90809-0999. (213) 597-2661.

May 19-22—**California Society of Anesthesiologists Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $225-$325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

CARDIOLOGY

January 21-23—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Fri-Sun. 20 hrs. Contact: American College of Cardiology, 9111 Old Georgetown Road, Bethesda, MD 20814-1699. (301) 897-2695.

January 28-29—**Coronary Heart Disease.** American College of Emergency Physicians at Las Vegas Hilton, Nevada. Fri-Sat. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

February 4-5—**Cardiology 1994: Concepts and Controversies.** Mercy Heart Institute at Radisson Hotel, Sacramento. Fri-Sat. $50. Contact: Mercy Heart Institute, (916) 733-6966.

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February 25-26—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sat. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

February 26—**Cardiology for the Primary Care Physician.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

February 26-March 5—**Cardiovascular Emergencies.** UCSD at Lahaina, Maui, Hawaii. 1 week. 21 hrs. $450. Contact: Edith Bookstein, (619) 454-3212.

March 25-26—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at MGM Grand, Las Vegas, Nevada. Fri-Sat. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

April 11-13—**4th Annual Symposium on Coronary Stenting.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 13-15—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Doubletree Resort, Palm Springs. Fri-Sun. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 3-5—**Pediatric Electrophysiology, Pacing Course and Board Review.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. $425. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

DERMATOLOGY

January 21-23—**Cutaneous Malignancies: 1994 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 17 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 21-23—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, (619) 223-2997.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Ruhenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

February 24-27—**Evaluation of Burn-Care Procedures Symposium 1994: Effects of Heparin in the Treatment of Burns.** UCSD at Marriott Hotel & Marina, San Diego. Thurs-Sun. Contact: Michael Saliba, (619) 454-9771.

March 18—**Current Issues in Dermatology.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

EMERGENCY MEDICINE

January 19-22—**The California Trauma Conference.** UCSF at San Francisco. Wed-Sat. Contact: UCSF.

January 22-29—**Update: Controversies in Emergency and Primary Care.** UCSD at The Royal Waikoloan, Kohala Coast, Hawaii. 1 wk. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 20-25—**Emergency Medicine 1994: 17th Annual UCD Winter Conference.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $495. Contact: UCD.

February 26-March 5—**Cardiac Emergencies.** UCSD at Royal Lahaina Resort, Maui, Hawaii. 1 wk. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 6-11—**14th Annual Mammoth Mountain Emergency Medicine Ski Conference.** American College of Emergency Physicians at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Daniel Abbott, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 14-18—**Emergency Medicine Symposium II.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

March 23-27—**Winter Wilderness Medicine: 1994.** American College of Emergency Physicians at Squaw Valley (Lake Tahoe). Wed-Sun. 21 hrs. $450. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 888-5632.

FAMILY PRACTICE/PRIMARY CARE

January 21-23—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 1-4—**HIV/AIDS and the Primary Care Practitioner—You Can Make a Difference.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Tues-Fri. 15 hrs. $365. Contact: UCD.

February 4-5—**Pediatric Dermatology for the Primary Care Physician.** UCSF and Stanford at Sheraton Palace Hotel, San Francisco. Fri-Sat. 10.5 hrs. $275. Contact: UCSF.

February 5-12—**5th Kaiser Permanente National Conference on Musculoskeletal Medicine.** Kaiser Permanente at Hyatt Regency, Kauai, Hawaii. 1 week. 29 hrs. $400. Contact: Ferdy Massimino, MD, 200 Muir Rd, Martinez 94553. (510) 372-1457.

February 12-14—**Colposcopy for the Primary Care Physician.** National Procedures Institute at Westin Maui, Lahaina, Hawaii. Sat-Mon. 12.25 hrs. $550. Contact: Linda Hallmann, 4909 Hedgewood Dr, Midland, MI 48640. (800) 462-2492.

February 18-20—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 18-21—**46th Scientific Assembly.** California Academy of Family Physicians at Doubletree/Marriott Hotels, Monterey. Fri-Mon. 28 hrs. $235. Contact: Christine Macpherson, (415) 394-9121.

March 18—**Cancer Detection and Follow-Up for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 19—**Emergencies in Primary Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 19—**Psychiatric Emergencies in Primary Care: A How To Primer.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20—**Outpatient Procedures for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20—**Urology for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 5.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 23-25—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $300. Contact: UCSF.

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March 28-31—**Primary Care in Paradise.** Scripps Clinic and Research Foundation at Princeville Resort, Island of Kauai, Hawaii. Mon-Thurs. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

April 21-24—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

May 5-7—**Primary Care for the '90s.** University of Nevada School of Medicine at Resort at Squaw Creek, Olympic Valley. Thurs-Sat. 15.5 hrs. $260-$290. Contact: University of Nevada, Manville Bldg/342, Reno, NV 89557. (702) 784-4605.

May 11-14—**16th Semi-Annual Wound Management for Primary Care Health Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $250-$475. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

May 13-14—**Coming of Age: Geriatrics for Primary Care Providers–Part 1.** UCD at Sacramento. Fri-Sat. Contact: UCD.

May 31-June 4—**21st Annual UCLA Family Practice Refresher Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Tues-Sat. 32 hrs. $485. Contact: UCLA.

June 12-17—**18th Annual Fingers to the Toes Orthopaedics for Primary Care.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. 25 hrs. Contact: UCD.

June 23-26—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 18 hrs. $370. Contact: UCLA.

1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

January 18-22—**11th Annual Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton Hotel, Beverly Hills. Tues-Sat. 44 hrs. $675. Contact: UCLA.

January 28-30—**Breakthroughs in Geriatric Psychiatry.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 17 hrs. $375. Contact: UCSD.

March 17-18—**Alzheimer's Disease Conference.** Advances in Treatment 1994. UCSD at Pan Pacific Hotel, San Diego. Thurs-Fri. 16 hrs. $195. Contact: UCSD.

March 20—**Long Term Care Update.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

INFECTIOUS DISEASES

February 4-5—**12th Annual Infectious Disease Conference.** UCD at Hilton Hotel, Sacramento. Fri-Sat. 11 hrs. $160. Contact: UCD.

INTERNAL MEDICINE

January 19-22—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt Islandia Hotel, San Diego. Wed-Sat. 25 hrs. $500. Contact: UCSD.

January 22—**Current Concepts in Hemostasis and Thrombosis.** UCD at Cancer Center Auditorium, Sacramento. Sat. 5 hrs. $25. Contact: UCD.

January 27-29—**Pulmonary Medicine and Surgery: New Approaches to Diagnosis and Treatment.** UCSD at San Diego Marriott Hotel and Marina. Thurs-Sat. 17 hrs. $475. Contact: UCSD.

February 3-5—**17th Annual Neurology for the Non-Neurologists.** UCSD at Pan Pacific Hotel, San Diego. Thurs-Sat. 21 hrs. $450. Contact: Edith Bookstein PO Box 2586, La Jolla 92038. (619) 454-3212.

February 5—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at Green Hospital Amphitheater. Sat. 7 hrs. $140. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 17-19—**Recent Advances in Neurology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $355. Contact: UCSF.

February 19-24—**Topics and Advances in Internal Medicine.** UCSD at San Diego Marriott Hotel, San Diego. Sat-Thurs. 52 hrs. $595. Contact: UCSD.

February 26-27—**Endoscopy 1994.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce M. Fried, 10833 Le Conte Ave, Los Angeles 90024-1722. (310) 374-9708.

March 4—**20th Annual Diabetes Symposium.** UCD at Sheraton Sunrise Hotel, Sacramento. Fri. 6 hrs. $130. Contact: UCD.

March 18-24—**Internal Medicine: 1994.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Thurs. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 17-19—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. 12 hrs. Contact: Karen Debont, 1500 W Canal Crt, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

OB/GYN

January 14—**OB/GYN Symposium.** San Jose Medical Center. Fri. 6 hrs. Contact: Theresa Goodnight, (408) 977-4490.

January 16-18—**Ambulatory Obstetrics and Gynecology.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Tues. 14.5 hrs. $300-$375. Contact: UCD.

February 17-20—**49th Obstetrical and Gynecological Assembly of Southern California** at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB/GYN Assembly of Southern California, 5820 Wilshire Blvd, $500, Los Angeles 90036. (213) 937-5514.

March 19—**Health Care Issues for Women Over 40.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 20-24—**Pacific Coast Fertility Society Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 17 hrs. Contact: Director, Continuing Medical Education, 15731 Imperial Hwy, Ste 427, La Mirada 90638-2510. (310) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

January 31-February 4—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. Contact: UCSF.

March 5-12—**Sports Medicine.** UCSD at Wailea, Maui, Hawaii. 1 week. 21 hrs. $450. Contact: UCSD.

March 19—**Practical Aspects of Occupational Medicine.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

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INTERNAL MEDICINE REVIEW

Oregon Health Sciences University

Portland, Oregon — May 19-21, 1994

This 2-1/2 day course offers a comprehensive review and update in all major medical subspecialties. Features include a wide range of workshop choices, ample opportunity for participant-faculty interchange, and an extensive course syllabus.

For more information please call J. Bachman at 1-800-452-1048.

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June 3-4—**Occupational and Environmental Medicine.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

ONCOLOGY

January 28-30—**46th Annual Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16.5 hrs. $450. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (310) 827-9078 or (800) 527-7013.

February 21-23—**Clinical Hematology and Oncology: 1994.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 30—**Cancer in Women: Management of Breast and Gynecologic Malignancies.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

OPHTHALMOLOGY

January 29—**General Medicine Update for the Ophthalmologist.** UCD at Cancer Center Auditorium, Sacramento. 6 hrs. $95. Contact: UCD.

March 20—**Ophthalmologist-Gatekeeper Interactions: Managed Eye Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott. (415) 882-3384.

May 21—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

ORTHOPEDICS

January 20-23—**Reconstruction of the Adult Hip: A Comprehensive Course.** American Academy of Orthopedic Surgeons at Hyatt Regency Maui, Lahaina, Hawaii. Thurs-Sun. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

January 23-26—**Fracture Management.** UCD at Resort at Squaw Creek, Squaw Valley. Sun-Wed. 15 hrs. $495. Contact: UCD.

January 27-30—**Spring Meeting of the Northern California Chapter of the Western Orthopedic Association** at Inn at Squaw Creek, Olympic Valley. Thurs-Sun. Contact: Iola Beckley, (707) 538-5548.

March 20—**Musculoskeletal Trauma in Children and Adolescents.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

1994—**Educational Program for Musculoskeletal Evaluation and Rehabilitation.** UCSD at La Jolla. 35.5 hrs. $500. Contact: UCSD.

OTOLARYNGOLOGY

January 16-21 and February 13-18—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

March 18—**Pediatric Otolaryngology: What Gatekeepers Need to Know.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 6-8—**Temporomandibular Joint Update.** UCD at Silverado Resort, Napa. Wed-Fri. 12 hrs. $300. Contact: UCD.

PATHOLOGY

March 18—**Skin Cancer: A Clinical and Histopathologic Update.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 16—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Fri. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

May 26-28—**10th Annual Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

PEDIATRICS

January 24-28—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $390. Contact: Center for Child Protection, 8001 Frost St, San Diego 92123. (619) 395-4950.

February 21-23—**Pediatrics Update 1994.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 19—**Pediatrics Emergencies.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 15-16—**Pediatric Dermatology for the Practitioner.** Children's Hospital and Health Center at L'Auberge Del Mar Hotel, San Diego. Fri-Sat. 12 hrs. $245. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

May 12-14—**27th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

June 1-3—**13th Annual Child Abuse and Neglect Conference.** UCD at Radisson Hotel, Sacramento. Wed-Fri. Contact: UCD.

June 24-26—**Current Concepts in Child Neurology 1994.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15 hrs. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

PSYCHIATRY

January 23-28—**20th Annual Midwinter Program in Continuing Medical Education for Psychiatrists.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

January 29—**Recovering Lost Ground: Optimal Mental Performance Strategies.** UCLA. Sat. 6 hrs. $115. Contact: UCLA Extension.

February 18-20—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 16 hrs. $475. Contact: UCSD.

February 26—**1994 Sleep Medicine Update.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5, 6, 19, 20—**Introductory Workshop in Clinical Hypnosis for Physicians, Dentists and Psychologists.** San Francisco Academy of Hypnosis at Alta Bates Hospital, Berkeley. Sat-Sun. 28 hrs. $375. Contact: San Francisco Academy of Hypnosis, Verna Carter, 29 Pinto Ave, San Francisco 94132. (415) 239-4104.

March 5-6—**Basic Hypnosis: A Hands-On Workshop.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 13 hrs. $295. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (310) 475-1260.

March 6—**Trance Patterns and Metaphors.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sun. 6 hrs. $150. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (310) 475-1260.

April 8-9—**West Coast Neuropsychology Conference: Part I.** UCSD at Pan Pacific Hotel, San Diego. Fri-Sat. 9 hrs. $175. Contact: UCSD.

April 9-11—**West Coast Neuropsychology Conference: Part II.** UCSD at Pan Pacific Hotel, San Diego. Sat-Mon. 14 hrs. $325. Contact: UCSD.

April 22-26—**The Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Colonial Inn, La Jolla. Fri-Tues. 26 hrs. $550. Contact: UCSD.

April 30-May 1—**Self Psychological Revolution: Psychotherapy Since Kohut.** UCSD at Pan Pacific Hotel, San Diego. Sat-Sun. 13 hrs. $325. Contact: UCSD.

1994—**Basic Clinical Hypnosis Training.** UCSD at La Jolla. Ongoing. 30 hrs. $245. Contact: UCSD.

RADIOLOGY

January 17-19—**Neuroradiology Update.** Stanford University Medical Center at Ritz-Carlton, Laguna Niguel. Mon-Wed. 17.5 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 20-23—**Breast Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 16 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 14-18—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 30 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 21-25—**Contemporary Diagnostic Imaging.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, Kapalua, Hawaii. Mon-Fri. 20.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925.

March 2-4—**14th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $350. Contact: UCSF.

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CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

JANUARY 28-30, 1994

KNEE SYMPOSIUM
LOCATION: Orlando, Florida
SPECIALTY: Orthopaedics
CME CREDIT: AMA Category I–11 hours
FEE: SMA Member-$140; Nonmember-$290; Residents/Fellows-$30

JANUARY 29-FEBRUARY 5, 1994

PREVENTIVE MEDICINE
LOCATION: Tucson, Arizona
SPECIALTY: Primary Care
CME CREDIT: AMA Category I–39 hours
FEE: SMA Member-$475; Nonmember-$600; Nonphysician-$300

FEBRUARY 2-4, 1994

ENT UPDATE
LOCATION: St. Thomas, Virgin Islands
SPECIALTY: Otolaryngology
CME CREDIT: AMA Category I–12 hours
FEE: SMA Member-$475; Nonmember-$600; Nonphysician-$300

FEBRUARY 8-13, 1994

THORACIC & CARDIOVASCULAR SURGERY
LOCATION: Grand Cayman Islands
SPECIALTY: Thoracic & Cardiovascular Surgery
CME CREDIT: AMA Category I
FEE: SMA Member-$375; Nonmember-$500; Nonphysician-$250

FEBRUARY 11-13, 1994

THE ATHLETIC PATIENT
LOCATION: Fort Lauderdale, Florida
SPECIALTY: Sports Medicine, Primary Care, Orthopaedics, Internal Medicine
CME CREDIT: AMA Category I–14 hours; AAFP Prescribed–14 hours; AOA Category 2-A–14 hours
FEE: SMA Member-$375; Nonmember-$500; Nonphysician-$250

FEBRUARY 17-19, 1994

4TH ANNUAL UPDATE IN MAMMOGRAPHY
LOCATION: Aruba
SPECIALTY: Radiology
CME CREDIT: AMA Category I–15 hours
FEE: SMA Member-$395; Nonmember-$520; Nonphysician-$275

MARCH 4-6, 1994

PHYSICAL MEDICINE & REHABILITATION
LOCATION: New Orleans, Louisiana
SPECIALTY: Physical Medicine, Physiatry, Orthopaedics
CME CREDIT: AMA Category I
FEE: SMA Member-$310; Nonmember-$435; Nonphysician-$225

MARCH 10-12, 1994

SEC SPORTS MEDICINE
LOCATION: Memphis, Tennessee
SPECIALTY: Orthopaedics, Family Practice, Sports Medicine
CME CREDIT: AMA Category I
FEE: SMA Member-$250; Nonmember-$400; Nonphysician-$125

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!

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March 4-6—**Women's Imaging Symposium: 1994.** UCSD at Catamaran Resort Hotel, San Diego. Fri-Sun. $495. Contact: UCSD.

March 7-10—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Thurs. 30 hrs. $625. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 19—**Dilemmas in Women's Imaging.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20-25—**UCLA General Radiology Review Course.** UCLA at Doubletree Hotel, Marina Del Rey. Sun-Fri. 40 hrs. $420. Contact: UCLA.

March 21-26—**Musculoskeletal and Neuro MRI.** UCSD at La Costa Resort and Health Spa, Carlsbad. Mon-Sat. 19.5 hrs. $550. Contact: UCSD.

April 3-8—**14th Annual Residents Radiology Review Course.** UCSD at Hotel Del Coronado, San Diego. Sun-Fri. 41 hrs. $450. Contact: UCSD.

April 9—**Interventional Radiology.** UCSD at Hotel Del Coronado, San Diego. Sat. 8 hrs. $135. Contact: UCSD.

April 17-22—**Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: UCSD.

1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

1994—**Visiting Fellowship Program of Endovaginal Sonography: Focus on Techniques and Application.** UCSD Medical Center. Monthly. 30 hrs. $600. Contact: UCSD.

SURGERY

January 14-15—**What's New in General Surgery.** UCD at Hyatt Regency Hotel, Sacramento. Fri-Sat. 15 hrs. $285. Contact: UCD.

February 11—**No-Scalpel Vasectomy.** National Procedures Institute at San Francisco Marriott Fisherman's Wharf. Fri. 5.5 hrs. $330. Contact: Linda Hallmann, 4909 Hedgewood Dr, Midland, MI 48640. (800) 462-2492.

February 12—**No-Scalpel Vasectomy.** National Procedures Institute at Los Angeles Airport Marriott. Sat. 5.5 hrs. $330. Contact: Linda Hallmann, 4909 Hedgewood Dr, Midland, MI 48640. (800) 462-2492.

March 24-25—**9th Annual Course in Colon and Rectal Surgery.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Thurs-Fri. Contact: Donna Bowker, 1975 Zonal Ave, KAM 307, Los Angeles 90033. (213) 342-2555.

March 24-26—**6th Annual Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

January 27-30—**Medicine Meets Virtual Reality II: Interactive Technology and Healthcare: Visionary Applications for Simulation, Visualization and Robotics.** UCSD at San Diego Marriott & Marina. Thurs-Sun. 21 hrs. $390. Contact: UCSD.

February 4-6—**Violence in America: Responding to the Crisis.** Kaiser Foundation Hospitals and Physicians for Violence Free Society at Mark Hopkins Hotel, San Francisco. 12 hrs. Contact: Jan Saga, (415) 821-5686.

February 6-11—**26th Annual CME/Ski Meeting.** Nevada Academy of Family Physicians at Harvey's Resort, Lake Tahoe. Sun-Fri. 39 hrs. Contact: Debi Bradley, PO Box 7471, Reno, NV 89510. (702) 826-5100.

February 12-13—**Clinical Applications of Vestibular Science.** UCLA. Sat-Sun. $350. Contact: Marjorie Harris, 15-50 Rehabilitation Center, UCLA 90024. (310) 825-5131.

February 14-18—**5th Annual Physician Heal Thyself.** UCSD at Palm Springs Hilton. Mon-Fri. 16 hrs. $395. Contact: UCSD.

March 20—**Risk Issues in Cost Contained Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 25-27—**63rd Clinical Conference.** Research Study Club at Huntington Ritz-Carlton Hotel, Pasadena. Fri-Sun. 15 hrs. Contact: Louise Ball, PO Box 1216, Murrieta 92564. (909) 677-4482.

June 24—**The Future of American Medicine: A Bioethics Symposium.** UCD at Sacramento. Fri. Contact: UCD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January 20-23—**The Psychobiology of Hypnotic and Dissociative States.** American Psychiatric Association and Colorado Psychiatric Society at Sonnenalp Hotel, Vail. Thurs-Sun. Contact: Karen Spalter, (303) 759-6045.

January 22-29—**Reconstructive Surgery of the Hip and Knee.** University of Colorado School of Medicine at Sheraton at Steamboat, Steamboat Springs. Sat-Sat. Contact: U of Colo.

January 23-29—**Fifth Annual Geriatrics Overview/ Board Review.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Sun-Sat. Contact: U of Colo.

January 27-29—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs and University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Thurs-Sat. Contact: Karen Babcock, (303) 393-2826.

January 29-February 5—**Internal Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 4-5—**Ninth Annual Rocky Mountain HIV Disease Conference.** University of Colorado School of Medicine at the Red Lion, Denver. Fri-Sat. Contact: U of Colo.

February 5-12—**General Surgery Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 12-19—**Emergency Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 12-19—**Psychiatry Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 19-26—**Neurology Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 19-26—**Obstetrics and Gynecology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 3—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Sat-Thurs. Contact: U of Colo.

February 26-March 4—**Crash '94 Colorado Review of Anesthesia.** University of Colorado School of Medicine at Radisson Resort, Vail. Sat-Fri. Contact: U of Colo.

February 26-March 5—**Pediatrics Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 5—**Infectious Disease Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Primary Care Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

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March 6-11—**14th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Continuing Education Center, (402) 559-4152.

March 12-19—**Sports Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 12-19—**Urology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 19-26—**Cancer Treatment Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

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(Continued on Page 24)

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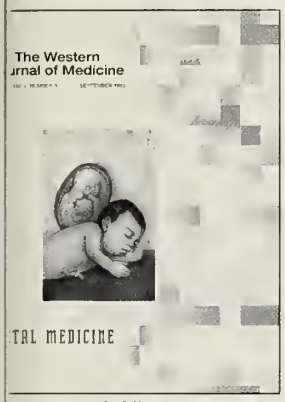

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- ETHICS OF FETAL TISSUE TRANSPLANTATION
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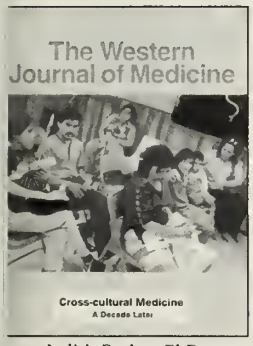

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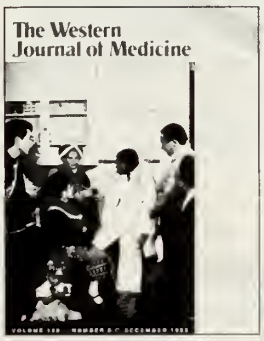

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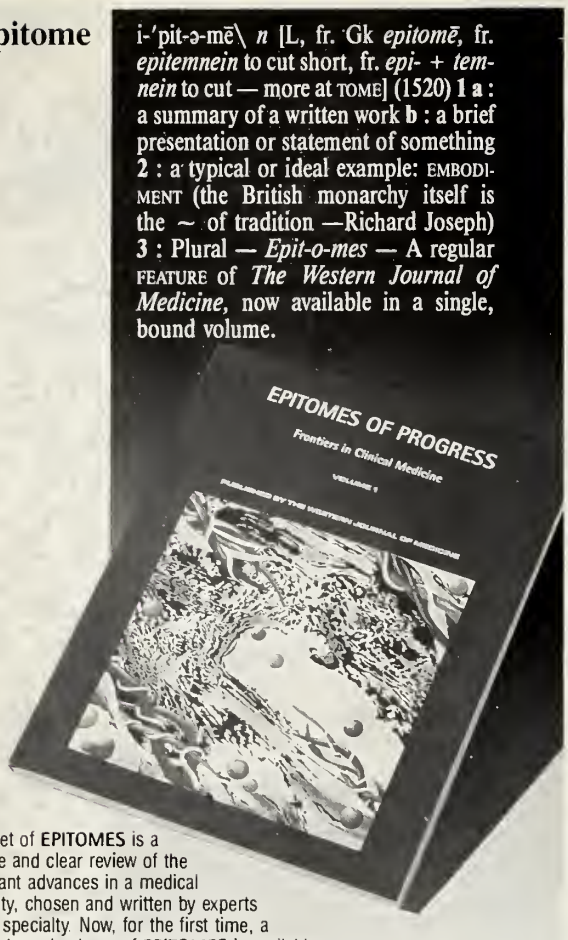

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IDAHO

February 18-20—**Ada County Medical Society—35th Annual Medical Winter Clinics—An Anthology of Clinically Relevant Topics for All Physicians.** Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. $125, Idaho Medical Society members; $175, nonmembers. Contact: Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930 or (208) 386-2135.

July 28-30—**Idaho Medical Association—Annual Meeting.** Sun Valley. Wed-Fri. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 6-7—**New Mexico Medical Society Annual Meeting.** The Marshall Building, Albuquerque. Fri-Sat. Contact: Elsa Hall, 7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237.

July 18-22—**Imaging 1994.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

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UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

January 19-22—**Midwinter Conference on Chest Disease.** Cliff Lodge, Snowbird. Wed-Sat. Contact: ITS.

January 29-February 5—**Richard Lende Winter Neurosurgery Conference.** Cliff Lodge, Snowbird. Sat-Sat. Contact: UANS.

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Articles

Peripherally Inserted Central Venous Catheters

Low-Risk Alternatives for Ongoing Venous Access

STEVEN W. MERRELL, MD; BONNIE G. PEATROSS, RN, MS; MICHAEL D. GROSSMAN, MD; JOHN J. SULLIVAN, PhD; *and* W. GRAYDON HARKER, MD, *Salt Lake City, Utah*

We prospectively evaluated the use of peripherally inserted central venous catheters to provide ongoing venous access in general medical and surgical patients in a Department of Veterans Affairs medical center. Between 1985 and 1988 trained nurses successfully inserted 393 catheters in 460 suitable patients (an 85.4% success rate). Correct catheter tip placement in the superior vena cava was documented in 359 of the 393 (91.3%) catheter insertions, but an additional 30 catheters were in a position deemed adequate for the intended use. The mean duration of catheter use was 27.6 ± 5.2 (1 standard deviation) days (median 20 days, range 1 to 370 days). A total of 65 patients left the hospital with catheters in place, with the mean length of catheter use at home being 36.2 ± 6.0 days (range 2 to 266). In all, 79% of the catheters were in use until the successful completion of therapy or patient death; catheter-related complications led to premature catheter removal in the remaining 21%. Catheter-related complications included bland phlebitis (8.2%), occlusion (8.2%), local infection (3.6%), bacteremia or fungemia (2.1%), mechanical failure or rupture (2.6%), venous thrombosis (0.7%), and other (3.3%). One patient required vein excision for the management of suppurative phlebitis, but no deaths were attributed to catheter use. This study illustrates the use and safety of peripherally inserted central venous catheters to provide reliable vascular access over prolonged periods in an elderly veteran population. At our facility, percutaneous central venous catheters and surgically implanted (Hickman or Broviac) catheters are now reserved for use in patients in whom peripherally inserted catheters cannot be placed.

(Merrell SW, Peatross BG, Grossman MD, Sullivan JJ, Harker WG: Peripherally inserted central venous catheters—Low-risk alternatives for ongoing venous access. West J Med 1994; 160:25-30)

Maintaining reliable vascular access in patients hospitalized long term can be difficult for both patients and their physicians. Many techniques have been developed for this purpose, including peripheral venous cannulas, arteriovenous fistulas, percutaneous central venous catheters, subcutaneously tunneled right atrial catheters, and peripherally inserted central venous catheters. Peripheral venous cannulas must be changed frequently, and access sites may be rapidly exhausted. Arteriovenous fistulas require an operative procedure, and the rate of complications has been unacceptably high when compared with other alternatives.[1] Percutaneous central venous catheters are uncomfortable, carry substantial risks associated with insertion, and usually require that patients are kept in the hospital during their use.[2] Tunneled catheters carry similar risks and also require surgical insertion.[3,4]

A useful alternative is the peripherally inserted central venous catheter (PICC), which was introduced in 1975.[5] This silastic catheter is inserted into a peripheral arm vein and passed centrally into the superior vena cava. The use of these catheters has gained wide acceptance for patients undergoing long-term cancer chemotherapy, total parenteral nutrition (TPN), and antibiotic therapy.[6-19] Peripherally inserted central venous catheters can be inserted at a patient's bedside or in an outpatient clinic and are immediately available for use once correct placement is confirmed. These catheters appear to be less thrombogenic than Teflon and polyethylene catheters, and their pliability helps ensure patient comfort.[20,21] Complications have generally been benign and can usually be treated without removing the catheter.

We present the results of our experience with the maintenance of 389 PICCs placed in patients in a Department of Veterans Affairs hospital from 1985 to 1988. The indications for catheter use and catheter removal, as well as associated complications in these patients, are presented.

Patients and Methods

In December 1984 we began a prospective evaluation of the applicability of PICC use in general medical and

From the Surgical (Drs Merrell, Grossman, and Sullivan), Nursing (Ms Peatross), and Medicine (Dr Harker) Services, Department of Veterans Affairs Medical Center and University of Utah School of Medicine, Salt Lake City.

Reprint requests to W. Graydon Harker, MD, Medical Service 111C, VA Medical Center, 500 Foothill Blvd, Salt Lake City, UT 84148.

ABBREVIATIONS USED IN TEXT

PICC = peripherally inserted central venous catheter
TPN = total parenteral nutrition

surgical patients at the Department of Veterans Affairs Medical Center in Salt Lake City, Utah, a 301-bed teaching hospital affiliated with the University of Utah School of Medicine. Before that time various methods discussed previously had been used to provide venous access for these patients, and no specialized services were available for teaching families, patients, or medical personnel regarding catheter care and maintenance.

Since 1984, patients with special needs for vascular access due to conditions such as insufficient peripheral venous access, cancer chemotherapy, long-term antibiotic therapy, and TPN, as identified by members of the medical and surgical house staff or attending staff at this facility, have been evaluated by nursing members of an informal vascular access team. Antecubital PICC insertion was attempted at the patient's bedside by one of three nurses specifically trained to insert silicone elastomer catheters (Intrasil, Baxter Health Care, Deerfield, Ill).

The Intrasil catheter is a single-lumen, 16-gauge catheter (inside diameter 0.1 cm [0.04 in], outside diameter 0.18 cm [0.07 in]) measuring approximately 51 cm (20 in) in length. Before catheter placement the desired length of the catheter was calculated to attempt to place the distal tip in the midsuperior vena cava. After placement, the catheter tip position was determined by chest x-ray study before use. A catheter tip in any location other than the superior vena cava was considered to be incorrectly positioned. In these cases, the catheter was either used at the discretion of the requesting physician or removed. If the catheter tip was in the correct position or the final site was adequate for use, the nurse secured the connector hub in the antecubital fossa using three nylon sutures. Sterile occlusive dressings were maintained over the entry site and changed twice a week. When not in use, the catheter was flushed daily with injections of heparin solution (100 units per ml) to maintain patency.

No restrictions were placed on the types of fluids that could be administered through the catheter or on its other uses, such as monitoring central venous pressure or drawing blood. Patients were observed by the vascular access nurses on a daily to weekly basis as needed during the hospital stay, with the daily catheter maintenance care provided by unit nurses. When PICCs were intended for outpatient use, catheter care instructions were given to the patient and family before discharge from the hospital or clinic. All outpatients with PICCs were monitored during subsequent clinic appointments and hospital admissions until the time of catheter removal or patient death. In general, catheter-related problems were brought to the attention of and managed by the vascular access nurses under the supervision of a physician.

Catheter occlusions were indicated by an inability to infuse fluid through or to withdraw blood from the catheter in the absence of obvious catheter kinking. Attempts were made by the house staff or the vascular access nurses to clear the occlusion by instilling 0.8 ml of urokinase (Open Cath, 5,000 units per ml, Abbott Laboratories, Chicago, Ill), as described elsewhere.[22] In accordance with the manufacturer's instructions, attempts were made to clear the catheter at times ranging from 5 to 60 minutes following urokinase instillation. Catheters that did not clear after one or two instillations of urokinase were removed and replaced if still needed. Other indications for catheter removal were completion of therapy; phlebitis, as evidenced by pain, tenderness, and erythema along the peripheral length of the catheter that did not respond to conservative measures, such as moist heat and elevation; subclavian vein thrombosis, verified by venography where possible; catheter rupture; catheter site infection that did not resolve with local treatment; and patient death.

If a fever of higher than 38.3°C developed after the catheter was inserted, a direct causal relationship between the presence of the catheter and the fever was considered, but the catheter was not empirically removed. In general, physicians were advised to obtain blood cultures through the catheter as well as from peripheral venous sites. Indications for catheter removal in these patients were the presence of septic thrombophlebitis or blood cultures positive for organisms either through the catheter or from peripheral sources. In most cases where fever persisted for 48 hours without a primary source of infection being identified, the catheter was removed at the discretion of the primary physician. In those instances, physicians were advised to culture the catheter tip upon removal. Otherwise, no attempts were made to routinely perform cultures of the catheter tip at the time of catheter removal.

Patient profile information and data regarding the attempted insertion sites, catheter tip location, and complications were stored in an IBM-PC/AT computer and analyzed with the Statistical Package for the Social Sciences (SPSS-X, SSPS Inc, Chicago, Ill). The incidence of the catheter-related complications noted above was compared with the indications for catheter use. Statistical differences between groups were determined with the Yates' χ^2, Fisher's exact, or two-tailed Student's t test. The null hypothesis was rejected when the P value was less than .05.

Results

Between December 1984 and August 1988, attempts were made to insert PICCs in 460 general medical and surgical patients at our facility. Patient characteristics are listed in Table 1. The mean patient age was 57.8 years (range 19 to 93). Only four women are represented in this group, which reflects the predominantly male veteran population at this facility. A total of 47 patients had more than one catheter placed during the period of study, with 1 patient having catheters placed on seven separate occasions. The clinical indications for catheter placement were antibiotic administration (48.7%), venous access (26.1%), parenteral nutrition (20.0%), and cancer chemotherapy (5.2%).

Antecubital veins were used for PICC insertion, with 44% of the catheters passed centrally through the cephalic

TABLE 1.—*Characteristics of 460 Patients Who Received Peripherally Inserted Central Venous Catheters*

Characteristic	Patients (n=460) No.	%
Age, yr	57.8*	19-93†
Sex		
Male	456	99.1
Female	4	0.9
Indication		
Antibiotic therapy	224	48.7
Venous access	120	26.1
Total parenteral nutrition	92	20.0
Chemotherapy	24	5.2
Site		
Left basilic vein	150	32.6
Left cephalic vein	95	20.7
Right basilic vein	103	22.4
Right cephalic vein	112	24.4
Insertion attempts	460	100
Successful insertions	393	85.4
Correct placement‡	359	91.3
Successful use§	389	99.0

*Mean.
†Range.
‡Catheter tip located in midsuperior vena cava; percentage calculated by dividing the number correctly placed by the number successfully placed.
§Catheter used for intended purpose; percentage calculated by dividing the number successfully used by the number successfully inserted.

veins and 56% through the basilic veins. All insertion attempts and repositioning efforts were directed at placing the catheter tip in the midsuperior vena cava. Of the 460 insertion attempts, 67 (14.6%) were unsuccessful, typically because of an inability to advance the catheter into a central venous location. Proper tip placement in the superior vena cava was documented in 359 of 393 patients (91.3%), and in the remaining 34 patients the final catheter tip location was elsewhere, such as the internal jugular or axillary veins, despite repositioning attempts. In 30 of these patients, however, the final location of the catheter was deemed adequate for the intended use. Thus, incorrect catheter position was responsible for an inability to use the catheter in only 1% (4 of 393) of the catheters inserted. Overall, PICC insertion successfully fulfilled the requirement for venous access in 84.6% of the patients (389 of 460) for whom long-term venous access was necessary. The number of insertion attempts and the percentage of catheters that could not be placed correctly are shown for each year in Figure 1. As can be seen, the catheter insertion success rate was relatively stable over the four-year period despite a gradual increase in the number of catheter insertion attempts.*

To determine if anatomical considerations were important in defining the catheter insertion success rate, we compared the rates of insertion success by side of attempt (left versus right) and by basilic versus cephalic sites of insertion. Technical success rates were significantly higher when the insertion was attempted at the basilic venous site compared with attempts made at the cephalic site (94.5% versus 86.4%, respectively; $P < .05$), but no differences were seen in the catheter placement success rates when compared by side of attempt.

Although most of the PICCs were inserted during a hospital stay, the catheters were intended for both inpatient and outpatient use in many of these patients. The mean duration of catheter use in the entire patient population was 27.6 ± 5.2 days (total 10,741 days, median 20 days, range 1 to 370 days). In all, 65 patients left the hospital with the PICC in place for continued outpatient use. The mean duration of catheter use in the outpatient setting was 36.2 ± 6.0 days (total 2,350 days, range 2 to 266 days). Despite the flexibility and small inside diameter of these catheters, little difficulty was encountered in the routine use of these catheters for drawing central venous blood.

Most of the catheters (64%) were removed after therapy was successfully completed (Table 2). An additional 14.9% were either removed at the time of a patient's death or were lost to follow-up when a patient was transferred to another facility. Thus, in 78.9% of these patients PICC placement allowed for successful completion of the prescribed treatment.

Catheter-related complications of a minor or serious nature were documented in 110 of 389 patients (28.3%) (Table 3). The major indication for premature catheter removal was the development of unexplained fever, which led to catheter removal in 25 patients. Although other complications, such as bland phlebitis and catheter occlusion, occurred more commonly (noted in 32 patients each), they did not necessarily lead to catheter removal. Bland phlebitis, which was characterized by local swel-

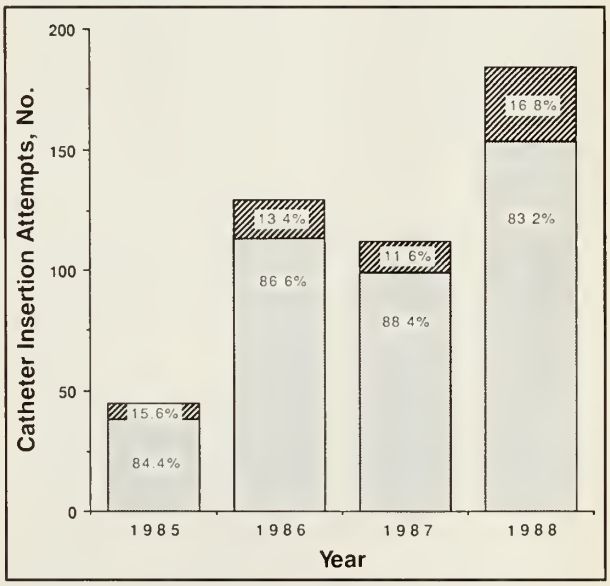

Figure 1.—The graph shows the number of peripherally inserted central venous catheter insertion attempts by year. Each bar is subdivided into the number of successful attempts (light hatch) and unsuccessful attempts (dark hatch), and within each hatched area is the percentage that that number represents of the total number of catheter insertion attempts for that year.

*Patricia Rushton, RN, PhD, and Sherry Brown, RN, assisted with inserting and maintaining catheters.

TABLE 2.—*Indications for Catheter Removal*

Indication	Patients No.	Patients %
Treatment completed	249	64.0
Death	54	13.9
Fever	25	6.4
Occlusion	14	3.6
Phlebitis	12	3.1
Ruptured catheter	10	2.6
Bacteremia or fungemia	8	2.1
Local infection	6	1.5
Transfer to other facility	4	1.0
Patient pulled out	3	0.8
Thrombosis	2	0.5
Unknown	2	0.5
Total	389	100.0

ling, erythema, and tenderness along the tract of the catheter, typically appeared during the first 24 to 72 hours after catheter insertion and in most cases resolved with moist heat. In 12 patients persistent phlebitis that did not resolve with local measures led to catheter removal. Urokinase instillation led to the restoration of patency in 18 of the 22 (81.8%) occluded catheters, whereas 4 catheters remained unusable despite urokinase administration and were subsequently removed. Ten catheters were removed because of catheter occlusion without an attempt being made to restore patency.

Fever led to catheter removal in 25 patients, but many of those patients had neither blood nor catheter tip cultures obtained. In all, 24 catheter-related infections were recorded in 21 patients. The onset of infection was documented at a mean of 32.5 ± 5.8 days after catheter insertion. Of the 21 patients, 14 had clinical evidence of a local catheter-related infection, many in the absence of fever. Three patients had evidence of local catheter site infection in association with bacteremia. The presence of fever (temperature > 38.3°C) and an erythematous, tender vein with purulent drainage at the catheter exit site led to the clinical diagnosis of suppurative phlebitis in two of the three patients, which occurred four and six days after catheter insertion, respectively. In both patients blood and catheter tip cultures were positive for the same organism, suggesting that the catheter was a possible source of the fever and bacteremia. One patient recovered after the catheter was removed and antibiotics administered. The other patient required surgical removal of the vein after catheter removal and parenteral antibiotics failed to control the infection. Two patients had minor infections at the suture site that resolved when the sutures were removed. In the remaining nine patients, the nurses described findings suggestive of minor local infections, such as tenderness and erythema, that were not confirmed by cultures. The signs and symptoms of infection cleared rapidly with aggressive local management in most of these patients, but the infection led to removal of the catheter in 6 of the 14 patients with local infection, including the 2 patients with suppurative phlebitis.

Bacterial or fungal cultures of peripheral blood specimens, catheter tips, or blood drawn through the catheter were positive in 10 of the 21 patients thought to have catheter-related infections. Bacteremia (6 patients) or fungemia (2 patients) was documented in eight patients in whom a PICC was present at the time of suspected systemic infection, with all eight growing the same organism from simultaneous blood and catheter tip cultures. Five of these patients had evidence of inflammation (erythema, tenderness, or both) at the catheter insertion site at the time that the bacteremia or fungemia was discovered, with two of the five displaying evidence of suppurative phlebitis as described earlier. The other three patients had no evidence of infection at the catheter insertion site. Four of the eight patients had documented infections at other sites involving lungs, bone, or urinary tract, which may have also served as sources for the bacteremia or fungemia. Two additional patients had positive cultures obtained at the time fever developed. One patient had bacterial growth in blood drawn through the catheter while simultaneous peripheral blood and catheter tip cultures were bacteriologically negative. In the other patient catheter tip cultures were bacteriologically positive at the time fever developed, but blood cultures were not obtained.

The bacterial species identified in the blood and catheter tip cultures were *Staphylococcus aureus* in four patients, *Klebsiella* species in three patients, and *Staphylococcus epidermidis* in one patient. Blood and catheter tip cultures from one patient grew the yeast form, *Torulopsis globrata*, whereas *Candida albicans* was cultured from both sources in another patient. Six of the nine patients with positive blood cultures, including both patients whose cultures grew yeast species, were receiving TPN at the time fever developed, whereas the remaining three patients were receiving antibiotics for previously established infections. Documentation of positive blood or catheter cultures in the setting of presumed systemic infection led to catheter removal and appropriate antibiotic therapy in ten patients. None died as a result of the presumed catheter-related infection.

Rupture of the catheter led to premature catheter re-

TABLE 3.—*Complications of Catheter Use in 389 Insertions*

Complication	Patients No.	Patients %
Bland phlebitis	32	8.2
Occlusion	32	8.2
Infection	24	6.2
Local	(14)	(3.6)
Bacteremia or fungemia	(8)	(2.1)
Other*	(2)	(0.5)
Catheter rupture	10	2.6
Venous thrombosis	2	0.5
Other (pain, bleeding)	10	2.6
Total	110	28.3

*Included 1 patient with a positive catheter tip culture only and 1 patient with a positive blood culture through the catheter but negative catheter tip and peripheral blood cultures.

moval in ten patients. In several instances the catheter was inadvertently penetrated during needle introduction through the cap, and in others the rupture was caused by the use of excessive force during attempts to clear catheter occlusion. In some cases no obvious explanation for the rupture was found. No cases of catheter embolization occurred.

Catheters were removed from two patients because arm swelling led physicians to suspect venous thrombosis. The presence of axillary vein thrombosis was confirmed by venography in one patient and was suspected in the second patient but not documented radiographically. Both patients had complete resolution of the arm swelling following catheter removal; only the patient with the abnormal venogram received heparin therapy.

To determine if any features of our patient population might identify patients at high risk of having a catheter-related complication we compared the incidence of complications by treatment indication subgroup—for example, chemotherapy versus TPN—and by patient age (60 years or older versus younger than 60), year of catheter insertion (1985-1986 versus 1987-1988), and site of insertion (left versus right, basilic versus cephalic). The incidence of bacteremia in patients with PICCs inserted specifically for TPN administration was significantly higher than in those patients in whom the catheters were used for other purposes (6.1% versus 1.0%, respectively; $P < .01$). Further analysis of the various patient subpopulations revealed no other factors that were associated with a significantly higher risk of having catheter-related complications.

Discussion

Providing long-term venous access through central venous catheters is accepted as standard practice in both surgical and medical patients. These catheters provide a route for the administration of fluids, chemotherapeutic agents, blood products, antibiotics, and total parenteral nutrition. In the past few years, the availability of several catheter types that vary in diameter, composition, lumen number, and mode of insertion has made the complication rates resulting from their use difficult to compare. The complication rates for percutaneously inserted central venous catheters of the tunneled variety have been reviewed recently,[1,23-25] but despite several years of experience with the peripherally inserted central venous catheters, no detailed descriptions of the complications resulting from the insertion of these catheters are available.

In this study, we have demonstrated that one particular PICC, the Intrasil catheter, is a safe and convenient alternative to other catheter types for providing long-term venous access for patients in a general medical or surgical service. Most of these catheters (75%) were inserted for use either in long-term antibiotic administration or to provide venous access; intravenous hyperalimentation was the indication for insertion in about 20% of the patients. In other reported series, the use of the PICC was limited to a particular population, such as patients receiving cancer chemotherapy[6,9,10] or TPN.[5,8,11] Thus, the variability in the complication rates noted in these reports may most accurately reflect differences in the study populations.

In our patients, the two most frequent complications associated with PICC use were phlebitis and catheter occlusion, both of which tended to be relatively minor and usually did not lead to catheter removal. Bland phlebitis, which typically occurred within two to three days of catheter insertion, usually resolved rapidly with local measures. The 8.2% incidence of phlebitis observed in this study is lower than the 23% incidence reported in early studies by Bottino and colleagues[6] but falls within the 1% to 10% range noted in more recent reports.[7,8,10-19] Suppurative phlebitis was noted in only two (0.5%) of our patients, and only one patient required vein excision. The incidence of suppurative phlebitis in the other reported series has been exceptionally low,[10-19] leading us to conclude that this is an unusual complication with these catheters.

Occlusion was noted in 8.2% of the catheters and was usually related to intravenous lines running dry. Catheter patency was rapidly reestablished in 82% of the catheters in which a fibrinolytic agent was used. Catheter occlusion rates in other descriptions of PICC use have ranged from 1.5% to 15%,[7-19] with many of the catheters being removed without an attempt to reestablish patency. A fibrinolytic agent routinely instilled into occluded PICCs, using methods described by Hurtubise and associates,[22] would make catheter occlusion an infrequent reason for premature catheter removal.

In a review of intravenous catheter-related infections, Hampton and Sheretz reported that the rate of catheter-related septicemia leading to systemic sepsis is low, occurring in less than 1% of patients.[26] Comparisons of the infection rates reported with various types of catheters are made difficult by differences in the definitions of "catheter-related infection," as well as by differences in the routine screening methods used to detect catheter colonization or infection. Peters and colleagues reported that bacterial colonization within or around any catheter probably begins almost immediately following catheter insertion.[27] Thus, the incidence of catheter-related infections reported in any series of patients will depend on the indications and techniques used for catheter tip culture and on whether blood specimens for culture were obtained through the catheter as well as from peripheral sites. In this series we noted local or systemic infections, or both, in 21 of 389 (5.4%) patients. A total of 14 patients had evidence of local infections, of which 8 responded to local care without catheter removal. In 10 patients (2.6%) bacteremia, fungemia, or positive catheter cultures led to catheter removal. Four of these patients had other sites of infection that may have been the source of bacteremia. Three patients had evidence of local catheter infection. The precise catheter-related sepsis rate cannot be determined in this study because of a failure to consistently obtain cultures of the catheter tip and blood before catheter removal or in all patients with unexplained fever.

A comparison of the catheter infection rate reported here with those from previous PICC studies is made difficult by the differences in definitions. Bottino and coworkers reported a 1% catheter-related sepsis rate in patients receiving long-term cancer chemotherapy.[6] Mills

and associates reported a single episode of staphylococcal sepsis in 61 patients in whom 67 PICCs (1.5%) had been placed for TPN administration,[13] whereas Roundtree reported only 2 catheter-related infections (positive tip cultures) during the use of 410 PICCs (infection rate < 0.5%) in patients in a general hospital setting.[15] In terms of infection rates per 100 days of catheter use, the patients in our series had a rate of 0.022 infections per 100 catheter days—24 infections during 10,741 days. This rate compares favorably with the rates of 0.1 to 1.9 infections per 100 days noted in other reported percutaneous catheter series and 0.00 to 0.18 infection per 100 days noted in patients with implantable catheter devices.[28] Thus, the incidence of local and systemic infections associated with the use of PICCs appears to be low and compares favorably with that seen during the use of other traditional catheter types.[28]

Special mention should be made of the ten catheters in this series that perforated or ruptured. The composition of these catheters makes needle penetration of the catheter wall easy during the process of gaining access through the rubber cap. Extra care must be taken to avoid catheter penetration during needle access and to avoid the use of excessive force during the process of clot dissolution. In the event that catheter rupture is confirmed, however, an alternative to removing the catheter would be to attempt to replace the catheter over a guidewire, as described by Lum and Soski.[29] The routine use of that technique in our patients might have obviated the need for reinserting the catheters in all ten patients.

Tunneled catheters of the Hickman or Broviac variety appear to be the gold standard in longevity for providing long-term central venous access. In a review of the complications associated with the use of Hickman catheters in patients with malignancy, Press and colleagues reported that the average duration of catheter use in 17 reported series was 92.4 days (range 15 to 120 days).[25] The average reported duration of PICC use has been in the 20- to 50-day range,[7-19] which is in keeping with the mean duration of 27.6 days noted in this series. The differences in average catheter dwell time between the two types are probably related to differences in the patient populations for which the catheters are targeted. Catheters of the tunneled variety are seldom inserted in patients in whom the projected need is for less than three to four months, whereas PICCs are chosen in those cases where either shorter durations of access are needed or double- or triple-lumen catheters are not required. Evidence that PICCs can be used for longer periods, if necessary, is provided by Legha and associates, who reported a median duration of catheter function of 238 days (range 2 to 521 days).[10]

In this series, PICCs were successfully placed and used in 85% of the patients who were identified as needing long-term venous access. Catheters remained in place for more than 70 days in 21 patients, with the longest period of use being 370 days. In 79% of the patients in whom a PICC was placed, the catheter successfully fulfilled the requirements for venous access for the duration of the identified need. Moreover, 16% of our patients were discharged with the PICC in place and were managed successfully as outpatients for an average of 36.2 days. This feature of PICCs offers a clear advantage over percutaneous central venous catheters and peripheral cannulas, which typically are less durable.

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Articles

The New Macrolides
Azithromycin and Clarithromycin

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Clarithromycin and azithromycin are among the new generation of macrolides that have recently been approved for use. Compared with currently available antibiotics, these agents may be given less frequently and, in the case of azithromycin, for a shorter duration. In vitro data suggest an antimicrobial advantage of both clarithromycin and azithromycin against atypical mycobacterial and toxoplasmal species and possibly *Haemophilus influenzae*. The cost of both these agents is substantially higher than that of erythromycin and doxycycline, although the convenience of single-dose azithromycin is appealing compared with a 7-day course of doxycycline for chlamydial urethritis and cervicitis. These agents appear to offer advantages over erythromycin in the treatment of *Mycobacterium avium-intracellulare*. Additional data are needed to establish their role in other bacterial infections.

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Erythromycin has been widely used in the treatment of pneumonias, including those caused by atypical organisms such as *Legionella pneumophila* and *Mycoplasma pneumoniae*.[1] Many of these pathogens multiply intracellularly and are resistant to standard β-lactam therapy. Erythromycin has limitations, a requirement for frequent doses, distressing gastrointestinal side effects, and reduced effectiveness after exposure to gastric acid.

To improve the spectrum of activity and decrease disadvantages, a new generation of macrolide compounds has been developed. These include azithromycin, clarithromycin, roxithromycin, dirithromycin, micocamycin, and rokitamycin. Azithromycin and clarithromycin have recently been approved by the Food and Drug Administration. Both appear to have more activity against *M pneumoniae*, *Haemophilus influenzae*, and *Chlamydia trachomatis*, among others, in addition to increased tissue or cellular penetration. They require less frequent dosing and may have fewer severe gastrointestinal side effects than erythromycin. In this review we summarize the pharmacology, spectrum of activity, and clinical use of azithromycin and clarithromycin.

Pharmacokinetics

Azithromycin and clarithromycin are different from the prototypic macrolide, erythromycin (Table 1). Erythromycin is acid labile. In the stomach, it rapidly decomposes to two inactive metabolites, one of which may contribute to the gastrointestinal side effects. As a result of this instability and depending on the salt form, the rate of absorption may be unpredictable (35% ± 25%).[2,3]

Clarithromycin is a 14-membered macrolide similar to erythromycin, whereas azithromycin is a 15-membered compound referred to as an azalide. Structural modifications prevent their degrading in an acid medium, so both have a more predictable oral bioavailability.

TABLE 1.—*Comparative Pharmacokinetic Variables of Erythromycin, Azithromycin, and Clarithromycin**

	Drug and Dose		
Variable	*Erythromycin, 500 mg*	*Azithromycin, 500 mg*	*Clarithromycin, 500 mg*
Oral bioavailability, %†...	35 ± 25‡	37	55 to 68
Taken with food	No	No	Yes
Serum half-life, hr§	1.5 to 3	11 to 14	4.9
Frequency of dosing, ×/day	4	1	2
Alter dose in moderate renal failure	Yes	No	Yes

*From Gilman et al[2]; Wilson and van Boxtel[3]; Neu[4]; Davey[5]; Ball[11]; and Lode.[12]

†Oral bioavailability refers to the fraction of the parent compound that reaches the systemic circulation.

‡Enteric-coated erythromycin base; absorption is dependent on the salt form and temporal relation to meals.

§The half-life is the time required for the plasma concentration in the body to decline by half.

Clarithromycin is rapidly absorbed from the gastrointestinal tract regardless of when taken and achieves peak serum concentrations in two hours. It has a predictable rate of absorption, and 55% to 68% is available in the serum. Food does not influence its bioavailability but slightly delays the time to peak concentration.[1,3-5] Clarithromycin is metabolized by the liver. One metabolite, 14-hydroxy-clarithromycin, has at least comparable and possibly better antimicrobial activity than the parent com-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CFU = colony-forming units
MIC_{90} = 90% minimal inhibitory concentration

pound.[5] The prolonged half-life of both clarithromycin and its 14-hydroxy metabolite allows for twice-a-day dosing. The renal clearance of clarithromycin and 14-hydroxy-clarithromycin approximates glomerular filtration.[5] Moderate to severe renal failure alters the clearance of both clarithromycin and its 14-hydroxy metabolite so that patients with a creatinine clearance of less than 0.50 ml per second (30 ml per minute) should have doses decreased by half.[6]

Azithromycin, like clarithromycin, is readily absorbed from the gastrointestinal tract and achieves peak serum levels within two hours. The bioavailability of azithromycin is substantially less than that of clarithromycin, about 37% to 40%. Food will decrease the bioavailability of azithromycin as much as 50%, so each dose should be taken at least an hour before or two hours after a meal.[7-9] It is metabolized by the liver, but unlike clarithromycin, its metabolites do not show notable antimicrobial activity. Azithromycin has an unusually long half-life so that once-a-day dosing is possible. High concentrations are achieved in tissue (skin, lungs, sputum, tonsils, and cervix). The extensive intracellular uptake of azithromycin results in a tissue half-life between two and four days.[8] In addition, azithromycin concentrates in polymorphonuclear leukocytes and phagocytes, suggesting that phagocytes may play a role in the transport of the drug to the site(s) of infection.[10] The intestinal tract is the major route of elimination for azithromycin; only 6% to 20% is eliminated renally.[11,12] Therefore, in patients with mild renal dysfunction, dose adjustment is not warranted. In patients with severe renal dysfunction, however, a decrease in dose or frequency of dosing intervals may be indicated.

Antimicrobial Spectrum

As a class, the macrolide antibiotics, specifically erythromycin, clarithromycin, and azithromycin, exert their antimicrobial activity by binding to the 50S subunit of the 70S ribosome, which interferes with protein biosynthesis of susceptible organisms.[1,4,13] Resistance is chromosome or plasmid mediated.

Overall, the microbiologic spectrum of the activity of clarithromycin and azithromycin mirrors that of erythromycin, with increased potency against certain pathogens (Table 2). The new generation of macrolides inhibits viridans streptococci, *Streptococcus pneumoniae,* and group A streptococci at readily achievable concentrations, similar to the action of erythromycin.[1,4,6,12,14,15] Streptococcal and staphylococcal species resistant to erythromycin are likely to be resistant to azithromycin and clarithromycin as well. *Moraxella catarrhalis, M pneumoniae, L pneumophila,* and *Chlamydia pneumoniae* are inhibited by azithromycin and clarithromycin at lower concentrations.

TABLE 2.—*In Vitro 90% Minimal Inhibitory Concentrations (MIC_{90}) of Erythromycin, Azithromycin, and Clarithromycin**

Bacterio	MIC_{90}, mg/liter		
	Erythromycin	Azithromycin	Clorithromycin
Borrelia burgdorferi	0.06	0.015	0.015-0.06
Compylobacter jejuni	1.0	0.12	2.0
Chlamydia pneumoniae	0.06	0.5	0.007
Chlamydia trachomatis	2.0	0.25	0.125
Hoemophilus influenzae	2.0-8.0	0.25-2.0	2.0-8.0†
Helicobacter pylori	0.25	0.25	0.03
Legionello pneumophilo	2.0	2.0	0.25
Moroxello cotarrhalis	0.25	0.06	0.12-0.25
Mycobocterium ovium-introcellulare	>64	32->64	4-16
Mycoplasmo pneumoniae	≤0.01	<0.01	0.5
Neisseria gonorrhoeae	0.25-0.5	0.03-0.06	0.25-0.5
Staphylococcus aureus	0.25	1.0	0.12
Streptococcus pneumoniae	0.015-0.25	0.015-0.25	0.015-0.06

*From Williams[16]; Brown et al[21]; Preac-Mursic et al[23]; Mursic et al[24]; and Ridgway et al.[25]
†The MIC_{90} of clarithromycin alone; 14-hydroxy, the metabolite, may contribute to antimicrobial activity.

Erythromycin is inactive against most gram-negative organisms (including *Escherichia coli* and *Salmonella, Shigella,* and *Pseudomonas* species). Similarly, both azithromycin and clarithromycin are ineffective against *Pseudomonas* species and most aerobic gram-negative bacilli, but azithromycin exhibits enhanced activity against *H influenzae* when compared with erythromycin. It is unclear whether this increased activity results in a reliable drug against *H influenzae.*[16] In one study, the persistence of *H influenzae* was shown in 5 of 21 patients treated for an exacerbation of acute bronchitis; all 5 patients required alternative antibiotic therapy.[17] Clarithromycin and its 14-hydroxy metabolite also appear to be moderately active against *H influenzae.*[18]

Both azithromycin and clarithromycin show promise in the treatment of atypical pathogens such as *Mycobacterium avium-intracellulare, Mycobacterium chelonei, Mycobacterium fortuitum, Borrelia burgdorferi,* and *Toxoplasma gondii.* Clarithromycin has been shown to inhibit *M avium-intracellulare* at concentrations achieved in both lung tissue and macrophages (90% of minimal inhibitory concentration [MIC_{90}] = 4 to 16 mg per liter), with enhanced activity when used in combination with rifampin and ethambutol hydrochloride.[19,20] Azithromycin is less active than clarithromycin against *M avium-intracellulare,* whereas other atypical pathogens such as *M chelonei* subspecies *chelonei* and *M fortuitum* biovariant *fortuitum* are more susceptible.[16,21] Because of high intracellular concentrations, however, azithromycin may still have in vivo effects against *M avium-intracellulare.*[22] In vitro, azithromycin and clarithromycin are active against *T gondii,* reaching sufficient concentrations in the cerebrospinal fluid to kill both active organisms and cysts.[6,16] Like erythromycin, both azithromycin and clarithromycin have shown in vitro activity against *B burgdorferi,* achieving an MIC_{90} of 0.015 and 0.015 to 0.06 mg per liter, respectively.[6,23,24] Because of their favorable kinetics and in

vitro efficacy, both azithromycin and clarithromycin warrant further evaluation in the treatment of mycobacterial infection, toxoplasmosis, and Lyme disease.

In vitro susceptibility of *C pneumoniae* (TWAR) to clarithromycin was compared with that of erythromycin, oxytetracycline, and the other new-generation macrolides.[25] Clarithromycin was found to be the most active, followed by erythromycin and azithromycin. Again, comparative controlled studies need to be done to confirm these in vitro findings.

Finally, both azithromycin and clarithromycin have shown in vitro activity against certain sexually transmitted diseases. Thus far, azithromycin has demonstrated moderate to excellent activity against *C trachomatis, Neisseria gonorrhoeae,* and *Ureaplasma urealyticum,* with cure rates of 91% to 97%.[26,27] Both azithromycin and clarithromycin have excellent in vitro activity against *Haemophilus ducreyi.* Clarithromycin has also shown in vitro bactericidal activity against *C trachomatis* and variable activity against *N gonorrhoeae.*

Clinical Trials

Clarithromycin

Clarithromycin has been evaluated in the treatment of several infectious diseases, including mild to moderate respiratory tract infection, skin or soft tissue infection, and infections due to *M avium-intracellulare* and *T gondii.* Its use has been compared with that of a number of agents—erythromycin, ampicillin, amoxicillin, and penicillin VK—in the treatment of community-acquired pneumonia, pharyngitis, or acute exacerbation of chronic bronchitis.[1,28] Two studies comparing clarithromycin with penicillin VK and one study comparing clarithromycin with erythromycin in the treatment of streptococcal pharyngitis showed clinical cure rates of 96% for clarithromycin and 89% to 96% for the other two agents. In comparative studies, clarithromycin was found to be well tolerated with no significant difference in the overall number of adverse events reported. In the erythromycin-treated group, however, a higher incidence of adverse drug reactions was observed, with 6.7% of patients requiring the discontinuation of therapy compared with 0.8% in the clarithromycin-treated group.[29-31]

Hamedani and co-workers studied 46 patients with confirmed *L pneumophila* pneumonia who were given clarithromycin, 500 to 1,000 mg orally twice a day for four weeks.[32] Of the 46 patients, 44 (96%) had received one or more antibiotics before study entry. Nearly three fourths (34) completed the study and were assessed for clinical and radiographic cure; bacteriologic cure was assessed in only 13 patients. A 98% cure rate was reported in the 34 patients who completed therapy. These results suggest that clarithromycin may be effective, but they need to be confirmed in larger controlled, comparative studies.

Cassell and colleagues conducted a double-blind, randomized, multicenter clinical trial comparing the use of clarithromycin with that of erythromycin in patients with community-acquired pneumonia.[33] A total of 120 patients received clarithromycin or erythromycin for 14 days. Clarithromycin and erythromycin were equally effective in the treatment of community-acquired pneumonia, with clinical cure rates of 83% and 87%, respectively. The frequency of adverse effects did not differ between the groups. The incidence of gastrointestinal side effects (vomiting, nausea, diarrhea, and dyspepsia), however, was greater for the erythromycin group (9 patients) than for those treated with clarithromycin (4 patients).

The safety and efficacy of clarithromycin have been evaluated in the treatment of skin or soft tissue infection.[22,34] One comparative trial involved 439 patients with pyoderma, cellulitis, wound infection, abscess, or folliculitis; causative agents included *Staphylococcus aureus* and *Staphylococcus pyogenes.*[22] Treatment with clarithromycin, erythromycin, or cefadroxil similarly cured or improved all groups of patients.

Clarithromycin appears promising in the treatment of disseminated *M avium-intracellulare.* In a randomized, placebo-controlled study, Dautzenberg and associates evaluated the ability of clarithromycin to decrease *M avium-intracellulare* bacteremia in patients with the acquired immunodeficiency syndrome (AIDS).[35] Fifteen patients were randomly assigned to one of two groups: group 1 was given clarithromycin, 1,000 mg orally twice a day for six weeks, followed by six weeks of placebo, rifampin, isoniazid, ethambutol, and clofazimine; group 2 was given placebo for only six weeks, followed by six weeks of clarithromycin plus the other four agents. The major determinant of efficacy was the quantitative difference of *M avium-intracellulare* colony-forming units (CFU) in blood between the two groups. During phase 1, blood cultures of seven of the eight patients receiving clarithromycin alone (group 1) became negative for *M avium-intracellulare* between weeks 2 and 4; one patient consistently had weakly positive blood cultures throughout this phase. The mean decrease in *M avium-intracellulare* bacteremia was 2.65 log. When these patients were switched to placebo plus the four-drug regimen, the blood concentration of *M avium-intracellulare* increased in four patients and remained undetectable in three patients. In the group initially treated with placebo (group 2), all five patients showed an increase in mean levels of *M avium-intracellulare* CFU by 1.55 log over six weeks. When group 2 patients were crossed over to clarithromycin plus the four-drug regimen, however, the mean *M avium-intracellulare* CFU levels of all patients decreased by 1.34 log over the six-week period. In another recent study by Dautzenberg and colleagues, the efficacy and antimycobacterial activity of high-dose clarithromycin (1,500 to 2,000 mg per day) were compared with those of low-dose clarithromycin (500 to 1,000 mg per day) in the treatment of disseminated *M avium-intracellulare.*[36] Bacteriologic cure was achieved in 63% and 98% of the patients in the low- and high-dose groups, respectively. An overall failure rate of 25% was seen between months 2 and 7 of treatment, however.

The use of clarithromycin in combination with pyrimethamine has been evaluated for the treatment of

acute toxoplasmal encephalitis in a study of 13 AIDS patients.[37] Clarithromycin, 2 grams per day, and pyrimethamine, 75 mg per day, were used. Eight patients completed the six-week regimen. Complete remission was defined as a resolution of all clinical or radiologic manifestations. Partial response was defined as 50% or more improvement of clinical or radiologic manifestations. Patients were evaluated at weeks 3 and 6; a complete remission of clinical symptoms was noted in six of eight patients (80%) and a partial response in two of eight patients (20%). The radiographic findings were less conclusive. In eight patients completing the course, a complete response was seen in one, a partial response in three, and an incomplete response in four patients. Mild nausea, vomiting, or skin rash (or all 3) occurred with the highest frequency (38%); these patients required no modification in their therapy. Two patients (15%) had clinical hearing loss that continued as long as two weeks after clarithromycin was discontinued. These data are comparable to the results reported for pyrimethamine plus sulfadiazine and pyrimethamine plus clindamycin.[38]

Azithromycin

The efficacy of azithromycin has been demonstrated in a limited number of clinical studies involving the treatment of sexually transmitted diseases, soft tissue infections, mild to moderate respiratory tract infection, and *M avium-intracellulare*.[22,26,39,40] Studies of animals suggest that azithromycin also may have a role in the treatment of *T gondii*.[41]

Considering its long pharmacologic half-life, azithromycin is promising in the treatment of infection due to *C trachomatis*, *N gonorrhoeae*, or *U urealyticum*. High levels of azithromycin have been observed as long as 96 hours after the administration of a single 500-mg oral dose, with a prolonged half-life of greater than 60 hours.[8] The maintenance of high tissue concentrations in uterine or cervical tissue may allow for single-dose treatment of pathogens such as *C trachomatis*.

A randomized, double-blind study compared three regimens of azithromycin with a seven-day course of doxycycline in the treatment of *C trachomatis*, *N gonorrhoeae*, and *U urealyticum*.[26] The doses of azithromycin were as follows: 500 mg orally twice a day for one day; 500 mg a day orally for one day, followed by 250 mg a day orally for two days; or 1 gram for a single dose. Patients were randomly assigned and observed for four weeks. The finding was that 92% of the patients with *N gonorrhoeae* infection and 96% of the patients with chlamydial infection were bacteriologically cured with azithromycin. Azithromycin was well tolerated (8 patients had either mild abdominal pain, nausea, or diarrhea) and may offer an alternative to doxycycline in the treatment of chlamydial infections.

A similar study of 108 patients confirmed the results of that study.[39] Patients with confirmed *N gonorrhoeae* or *C trachomatis* infections or both were treated with single-dose or three-day regimens of azithromycin compared with a seven-day course of doxycycline (100 mg orally twice a day). Single-dose azithromycin treatment was as effective as the standard seven-day doxycycline therapy against *C trachomatis*. It is unclear whether a single 1-gram oral dose may be recommended as an alternative treatment of uncomplicated gonorrhea; ongoing studies are attempting to answer this question.

Comparative trials have evaluated the clinical efficacy of azithromycin in skin or soft tissue infection.[39,42] Treatment with azithromycin (500 mg every 12 hours for 1 day, then 250 mg a day on days 2 to 5) was compared with that of erythromycin (500 mg every 6 hours for 7 days) in 69 patients diagnosed with pyoderma, abscess, or infected wounds, among other infections. Clinical cure or improvement was achieved in 86% of the azithromycin-treated group and 82% of the erythromycin-treated group. Bacteriologic eradication was achieved in about 60% of all patients. *S aureus* was the most common organism isolated.

In a second randomized, third-party-blinded trial, the use of azithromycin was compared with that of cephalexin in the treatment of skin and skin structure infections.[42] The main causative agents in the 361 patients entered in the study were *S aureus* and *S pyogenes*. As in the previously described study, if the pathogens were resistant to therapy or a causative agent was not identified, the patients were withdrawn from the study. Patients were randomly allocated to receive azithromycin, 500 mg orally for one day followed by 250 mg orally a day on days 2 to 5, or cephalexin, 500 mg twice a day for ten days. Of the 149 patients evaluated, clinical cure was achieved in 66.7% of the azithromycin-treated group and 58.7% of the cephalexin-treated group. The bacteriologic cure rate was 98% in both groups. Similar to the previous trial, the large withdrawal rate complicates analysis. Furthermore, the cure rate was not stratified by primary diagnosis. Additional comparative trials are needed to define the usefulness of azithromycin in the treatment of skin and soft tissue infection.

Azithromycin has been compared with other agents in the treatment of upper respiratory tract infections. Azithromycin, 500 mg orally on day 1, followed by 250 mg orally on days 2 to 5, was compared with penicillin VK, 250 mg orally four times a day for ten days, in the treatment of streptococcal pharyngitis.[43] Clinical cure occurred in 86.8% of the patients receiving azithromycin and 78% of the patients taking penicillin VK. Complete eradication of group A β-hemolytic streptococci was achieved in 90% of the azithromycin-treated group and 95% of the penicillin-treated group.

Likewise, a second study evaluated the efficacy of azithromycin (500 mg orally on day 1, followed by 250 mg orally on days 2 to 5) with that of erythromycin (250 mg orally 4 times a day for 10 days) and amoxicillin (500 mg orally 3 times a day for 10 days) in the treatment of sinusitis and other upper respiratory tract infections.[44] Clinical cure was achieved in 82% of the patients receiving azithromycin compared with 79% and 87% of the erythromycin- and amoxicillin-treated pa-

tients, respectively; this included an 89% to 91% eradication of *H influenzae*.

Azithromycin has also been evaluated in the treatment of lower respiratory tract infections. When compared with erythromycin (500 mg orally 4 times a day for 7 to 10 days) or amoxicillin (500 mg orally 3 times a day for 7 days), azithromycin achieved clinical cure rates of 51% to 70% compared with 60% for erythromycin and 45% for amoxicillin.[45] Bacteriologic eradication of the main pathogens (*H influenzae, S pneumoniae*, and *S aureus*) was comparable among the three groups (76% to 85%); this includes an *H influenzae* eradication rate of 81% to 86% (azithromycin) and 78% to 80% (amoxicillin and erythromycin). Adverse effects, the most common of which were nausea, vomiting, and diarrhea, occurred in 5% of all patients treated with azithromycin compared with 18% of the erythromycin-treated patients. Considering the lack of data in the treatment of lower respiratory tract infection, the manufacturer recommends that azithromycin not be used in the following persons: patients with nosocomially acquired infection, patients with known or suspected bacteremia, patients requiring hospital admission, elderly or debilitated patients, and patients who are immunocompromised.

Schönwald and co-workers compared the efficacy of azithromycin with that of erythromycin in the treatment of pneumonia due to *M pneumoniae* and *Chlamydia psittaci*.[40] In that study, 57 patients were treated with azithromycin and 44 patients were treated with erythromycin. The investigators concluded that a five-day regimen of azithromycin was equally efficacious to a ten-day course of erythromycin.

Despite the poor in vitro activity of azithromycin against *M avium-intracellulare* (Table 2), the drug may be effective because of the high tissue concentrations achieved with this agent. In one uncontrolled study, Young and colleagues showed that azithromycin given in doses of 500 mg orally a day for as long as 30 days substantially reduced the degree of mycobacteremia.[22] Although this was a small study (n = 24) and involved single-drug therapy for a short period of time, it suggests the effectiveness of azithromycin in treating *M avium-intracellulare*.

In the murine model, azithromycin therapy has been noted to prevent death due to *T gondii*.[41] The concentration needed to achieve the appropriate MIC_{90} appears to be toxic to host macrophages.[46] Clinical trials using a combination of pyrimethamine and azithromycin are currently under way.[14]

Adverse Effects

Structural modifications of the newer generation of macrolides render them more acid stable, with fewer side effects when compared with erythromycin.[26,32,33,39,40] Gastrointestinal side effects (diarrhea, nausea, abdominal pain, dyspepsia, vomiting, or gastritis) have been reported in 10% to 20% of clarithromycin-treated patients and 10% of azithromycin-treated patients compared with 20% to 35% with erythromycin.[11,28,33] Anderson evaluated adverse effects in 3,437 patients who had received clarithromycin in phase II-III studies and found an incidence of mild to moderate adverse effects; 1% were classified as severe.[28] In the limited number of clinical trials evaluating the efficacy of azithromycin, the incidence of side effects ranged from 0% to 8%, with abdominal pain, nausea, and mild diarrhea the most frequently reported.[26,39,40] Hopkins and associates studied the tolerability and safety profile of azithromycin in approximately 4,000 patients.[9] Side effects were reported in 12% of the patient population. Gastrointestinal side effects (diarrhea, abdominal pain, and nausea) predominated. Central and peripheral nervous system adverse effects (headache, dizziness, fatigue) were noted, but they were mild to moderate in severity.

Anecdotal data suggest that the newer macrolides (especially clarithromycin) may exhibit teratogenic effects. Four unpublished studies of animals using clarithromycin describe adverse effects on embryofetal development. These effects include growth retardation, cleft palate, and cardiac defects. Based on these data, the manufacturer recommends that clarithromycin be used in pregnant women only where no alternative therapy is appropriate.[13]

Likewise, multiple doses of azithromycin have also been tested for teratogenicity in mice and rats.[47] To date, no teratogenicity or effects on fertility have been observed in either species. No studies have been done of pregnant women.

Drug Interactions

Because clarithromycin and azithromycin have only recently gained Food and Drug Administration approval, information regarding clinically important drug interactions is limited (Table 3). The use of erythromycin has been associated with a number of drug interactions involving theophylline, carbamazepine, warfarin sodium, digoxin, and ergotamines.[1,13] The mechanism of action involves the inhibition of drug metabolism by the cytochrome P-450 mixed-oxidase system, thus leading to increased drug concentrations.

Ruff and co-workers, in evaluating the possible interaction between clarithromycin and theophylline, found that clarithromycin increased the mean steady-state theophylline concentration from 86 to 102 μmol per liter.[48] It was concluded that concurrent administration is not an absolute contraindication, but caution must be taken in those patients with concentrations in the upper therapeutic range or in those who are sensitive to minor fluctuations in theophylline levels. Of the 3,437 patients involved in phase II-III trials of clarithromycin, 18% received one or more concomitant medications (not listed) whose oxidative metabolism may have been affected by clarithromycin.[49] There was no increase in the incidence of adverse effects reported in this patient population, with the exception of persons receiving concomitant theophylline; 9 of 492 of these patients had a mild to moderate drug interaction with theophylline.

Azithromycin, like erythromycin, interacts with the cytochrome P-450 system. To date, however, no clinically notable drug interactions have been reported with

TABLE 3.—*Drug Interactions With Erythromycin, Azithromycin, and Clarithromycin**

Interacting Drug	*Erythromycin*	*Azithromycin*	*Clarithromycin*
Digoxin	Increased digoxin levels	Not reported but the potential exists	Not reported but the potential exists
Anticoagulants (warfarin sodium)	Increased therapeutic effects (prothrombin time and international normalized ratio)	Not reported but the potential exists	Not reported but the potential exists
Ergotamines	Possible severe peripheral vasospasm; dysesthesia	Possible severe peripheral vasospasm; dysesthesia	Not reported but the potential exists
Triazolam	Increased pharmacologic effect of triazolam	Not reported but the potential exists	Not reported but the potential exists
Magnesium or aluminum antacids	May increase the half-life of erythromycin	Decreased peak serum levels without affecting the extent of absorption	Not reported but the potential exists
Carbamazepine, phenytoin, cyclosporine, hexobarbital, theophylline	Possible increase in serum levels	Not reported but the potential exists	Phase I studies: demonstrated increased plasma levels of theophylline and carbamazepine

*From Hopkins[9] and the product package insert for Ery-Tab (erythromycin), Abbott Laboratories, North Chicago, Ill.

theophylline, warfarin, carbamazepine, or methylprednisolone sodium succinate.[9,12] Furthermore, in those clinical studies in which azithromycin-treated patients received concomitant medications—bronchodilators, analgesics, corticosteroids, diuretics, hypnotic or sedative anxiolytics, or antiarthritis drugs—no drug interactions were noted. These observations, however, should not preclude the careful monitoring of patients for possible drug-induced interactions. It is unknown whether either azithromycin or clarithromycin interacts similarly to erythromycin with other drugs.

Potentially serious interactions may involve certain highly protein-bound drugs because the macrolide antibiotics extensively bind to the α_1-acid glycoproteins. Theoretically, the displacement of bound drug may result in increased free concentrations and thus an increased pharmacologic effect.

Costs

Whereas the newer macrolides offer the advantages of less frequent dosing and better gastrointestinal tolerability, they are considerably more expensive than erythromycin. Table 4 compares the cost of various treatments with these drugs.

Conclusion and Recommendations

Azithromycin and clarithromycin offer microbiologic advantages over erythromycin, particularly against atypical mycobacteria and *T gondii*. Although the clinical data are limited, these drugs appear to have some use in the treatment of disseminated *M avium-intracellulare* in AIDS patients and as an alternative therapy for central nervous system toxoplasmosis. Whereas azithromycin and clarithromycin appear to be more active against *H influenzae*, it is unclear whether these drugs offer additional benefit over erythromycin. Clinical data are insufficient to establish these drugs as alternatives to combination agents such as trimethoprim-sulfamethoxazole or amoxicillin-clavulanate in the treatment of community-acquired respiratory tract infection due to *H influenzae*. The prolonged half-lives of these agents result in less frequent dosing. This benefit is most obvious for azithromycin in which a single dose is as effective as one week of doxycycline in the treatment of uncomplicated chlamydial cervicitis and urethritis. Limited studies also suggest that five days of azithromycin therapy may be as effective as more prolonged courses of alternative antimicrobials in skin and soft tissue infection and mild respiratory tract infection. The newer agents appear to be better tolerated by the gastrointestinal tract than erythromycin, but the incidence of adverse effects may differ with the salt form of erythromycin. Finally, azithromycin and clarithromycin are more expensive than erythromycin. Until additional clinical data become available, azithromycin and clarithromy-

TABLE 4.—*Dosage Regimens and Comparative Cost**

Dosing Regimens	*Total Cost, $†*
Upper respiratory tract infection	
Sulfamethoxazole-trimethoprim (800/160 mg) 2×/d for 10 d	2.00
Erythromycin, 500 mg every 6 hr for 10 d	10.00
Clarithromycin, 500 mg every 12 hr for 10 d	53.40
Azithromycin, 500 mg a day for 1 d followed by 250 mg a day for 4 d	48.72
Lower respiratory tract infection	
Sulfamethoxazole-trimethoprim (800/160 mg) 2×/d for 10 d	2.00
Erythromycin, 500 mg every 6 hr for 10 d	10.00
Clarithromycin, 500 mg every 12 hr for 10 d	53.40
Azithromycin, 500 mg a day for 1 d, then 250 mg a day on days 2 to 5	48.72
Sexually transmitted diseases	
Doxycycline, 100 mg 2×/d for 7 d	1.96
Azithromycin, 1,000 mg for 1 dose	32.50
Skin or soft tissue infections	
Erythromycin, 500 mg every 6 hr for 7 d	7.00
Cephalexin, 500 mg 4×/d for 10 d	35.60
Clarithromycin, 250 mg 2×/d for 10 d	53.40
Azithromycin, 500 mg for 1 dose, then 250 mg a day for 4 d	48.72

*From the product package inserts of Biaxin (clarithromycin), Abbott Laboratories, North Chicago, Ill, and Zithromax (azithromycin), Pfizer Laboratories, New York, NY.
†Based on the Average Wholesale Price Blue Book.[50]

cin should be considered only in those patients intolerant of erythromycin or doxycycline or in AIDS patients with disseminated *M avium-intracellulare* infection.

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Articles

A Rural Emergency Department

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The appropriate use of emergency departments is of growing concern. By knowing which patients are more likely to make inappropriate visits to these departments, efforts can be directed to encourage more suitable care. Our study was done in a rural county hospital in eastern New Mexico. Data were collected from all emergency department visits over a 4-week period. Patient and physician questionnaires were administered to assess aspects of emergency department use, including appropriateness based on published criteria, physicians' opinion of appropriateness, groups who made inappropriate visits, and the perception of the need for and the urgency of a visit. We found that 32% of visits were inappropriate based on published criteria and 24% were considered inappropriate by physician opinion. Two groups with a high rate of inappropriate visits were Hispanics and Medicaid recipients. Patients and physicians have differing opinions of the urgency of a visit and of how soon medical treatment is required. To decrease the frequency of inappropriate use of emergency departments, educational efforts should be focused on the subgroups with high rates of such use.

(Frey L, Schmidt J, Derksen DJ, Skipper B: A rural emergency department. West J Med 1994; 160:38-42)

What is an emergency? The answer depends on whom you ask, whether it be a patient or a physician. In numerous studies done to determine appropriate emergency department (ED) use, various criteria were used to determine appropriateness, such as "threat to life and limb" and physician opinion,[1,2] but most did not take into account patients' perception of an emergency. The American College of Emergency Physicians sees this as an important element in determining an appropriate ED visit. In a 1982 policy statement by the American College of Emergency Physicians, a visit to an ED was appropriate in the following circumstances[3(p672)]:

> An unforeseen condition of a pathophysiological or psychological nature develops which a prudent lay person, possessing an average knowledge of health and medicine, would judge to require urgent and unscheduled medical attention most likely available, after consideration of possible alternatives, in a hospital emergency department.

Appropriateness, ED population demographics, and patient and physician perceptions are the subjects of this study. Because patients' and physicians' definitions of emergency may differ, it is predictable that their perceptions of the urgency of a visit and the time frame for the need of treatment would also differ. We attempt to quantify these differences. Although previous studies have examined various aspects of ED use, most have been conducted in large hospitals in urban areas. This study is unique in that it was carried out in a rural county hospital in eastern New Mexico.

Using a prospective study design, we examined several aspects of ED use: the appropriateness of visits as determined by criteria and physician opinion, subgroups with a higher-than-average number of inappropriate visits, and the differences between patients' and physicians' perceptions of the urgency of a visit and the time frame needed for treatment.

This study was conducted at the ED of the county hospital, Roosevelt General Hospital, in Portales, New Mexico. This 40-bed hospital is the only hospital in the county. The next closest hospital is in Clovis, New Mexico, about 20 miles away. Visits to the ED of Roosevelt General Hospital in 1991 totaled 6,210, with a mean of 17.0 visits per day. Portales has a population of about 11,000 in a rural county of 17,000. There are 13 physicians in the city, all of whom see Medicare and Medicaid patients in the ED. If a physician is on duty for the ED, a patient is seen regardless of ability to pay. The ED is staffed by seven family practice physicians (5 are board certified) and two internal medicine physicians (1 is board certified). The only additional required training is advanced cardiac life support.

Methods

Data were collected from all ED visits during a four-week period from June 8, 1992, to July 6, 1992. To compile data for this study, patient and physician questionnaires were developed, and criteria for an appropriate ED visit were adopted. The patient survey consisted of five questions, which included the patient's perception of the urgency of the visit (scaled from 1 to 10), the patient's perception of how soon the care was needed (minutes,

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hours, days), the reason(s) for the ED visit, and whether the ED or a physician was notified before the ED visit. The physician survey consisted of the following questions: the physician's perception of the appropriateness of the visit, the perceived urgency of the visit (scaled from 1 to 10), and the physician's perception of how soon the care was needed (minutes, hours, days).

The criteria used to determine appropriateness were based on the American College of Emergency Physicians guidelines reference and on a modification of a previous study by Buesching and co-workers.[3] A visit was considered appropriate if it fulfilled one of the following criteria: an acute condition—abdominal pain, fracture, headache present less than 48 hours—occurs suddenly; chest pain is the chief symptom; fever greater than 38.8°C is present in an adult or 39.4°C in a child and has been present less than 48 hours; the patient is being admitted or transferred to the hospital; the patient was brought by ambulance; the patient has a laceration; a chronic condition, such as chronic obstructive pulmonary disease, has acutely exacerbated; or the patient is referred to the ED by a physician.

Additional information was collected from the patients' ED admission sheets, including age, sex, race or ethnicity, town of residency, the primary payer (Medicare, Medicaid, private insurance, or self), time and day of visit (office hours were considered to be 9 AM to 5 PM), body temperature, chief complaint, diagnosis, admission to the hospital, attending physician, and whether the patient was brought in by ambulance.

Patients were asked by the ED personnel to complete the questionnaire before being evaluated by a physician. If a patient was unable to fill out the questionnaire, it was completed by the party who accompanied the patient. The physician questionnaire was completed by the attending physician after the visit. We evaluated each visit using the predetermined criteria.

Descriptive analyses were compiled using the SAS statistical package. χ^2 Tests were used to test the relationship between the appropriateness of a visit and other factors such as demographic characteristics. Logistic regression was used to estimate the effects of age, ethnicity, and primary payer on the occurrence of inappropriate visits. The largest sample sizes for these characteristics were for the categories 20 to 39 years old, Non-Hispanic White, and Insurance, which were chosen as the reference categories.*

Results

There were 466 visits to the ED during the time period of the study. Of those 466 visits, 49 were excluded from further study because the patient came to the ED for the administration of medications (patients with standing orders), was sent by a physician for a procedure that could not be done in the office (casting or obtaining x-ray films), or left for a physician's office without being seen in the ED. Appropriateness data were collected for the remaining 417 visits. Patient questionnaires were complete for 326 (78%) and physician questionnaires for 390 (94%) of the 417 visits. For 316 (76%) of the visits, both patient and physician questionnaires were complete.

Characteristics and demographics of the ED population were compiled on all 466 patients. Male patients totaled 208 (44.7%), and female patients totaled 257 (55.3%). Of all visits, 25.4% were made by patients between the ages of 20 and 39 years. About a third of the visits (34.2%), however, were made by patients older than 40 years. The median age was 28 years. In all, 60% of the patients were non-Hispanic white, and 37.4% were Hispanic. The primary means of payment for 34.9% of the visits was private insurance. Medicaid and Medicare accounted for 28.0% and 19.8% of the primary payers, respectively. Visits were well distributed throughout the week, ranging from 11.6% on Wednesday to 17.2% on Sunday. A total of 186 of the visits (39.1%) occurred on the weekends (from 5 PM Friday to 8 AM Monday). The number of visits during office hours is less than that reported in other studies (Table 1).[4,5]

The demographic data of the general population of Roosevelt County and the ED population from the county were compared to identify which subpopulations used the ED most often (Figure 1).

According to the predetermined criteria, 285 visits (68.3%) were appropriate, with the remaining number (132, or 31.7%) considered inappropriate. Physicians, however, reported that 75.6% of the visits were appropriate with 24.4% being inappropriate (Figure 2). These differences are statistically significant ($P < .0001$). Out of 394 visits, both physicians and the Buesching criteria classified the visit as appropriate 255 times (65%) and as inappropriate 77 times (20%), giving an overall rate of agreement between physicians and the Buesching criteria of almost 85%.

TABLE 1.—*Characteristics of the Emergency Department Population (n = 466)*

Characteristic	Patients, No.*	Patients, %
Primary payer		
Self	80	17.2
Medicare	92	19.8
Medicaid	130	28.0
Insurance	162	34.9
Time of visit		
Office hours (9 AM-5 PM)	122	26.2
After hours	158	33.9
Weekend	186	39.9
Residence		
Portales, New Mexico	373	81.6
Roosevelt County (not including Portales)	27	5.9
Other New Mexico	36	7.9
Out-of-state	21	4.6

*The total number of patients differs among categories because not all survey questions were answered.

*Lori Lambert, Department of Family and Community Medicine, University of New Mexico School of Medicine, Albuquerque, provided statistical assistance.

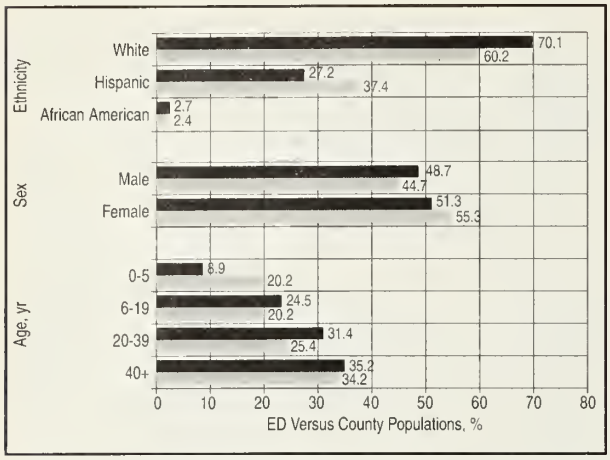

Figure 1.—The graph compares the general population of Roosevelt County (black bars) with the emergency department (ED) population (screened bars) by race, sex, and age.

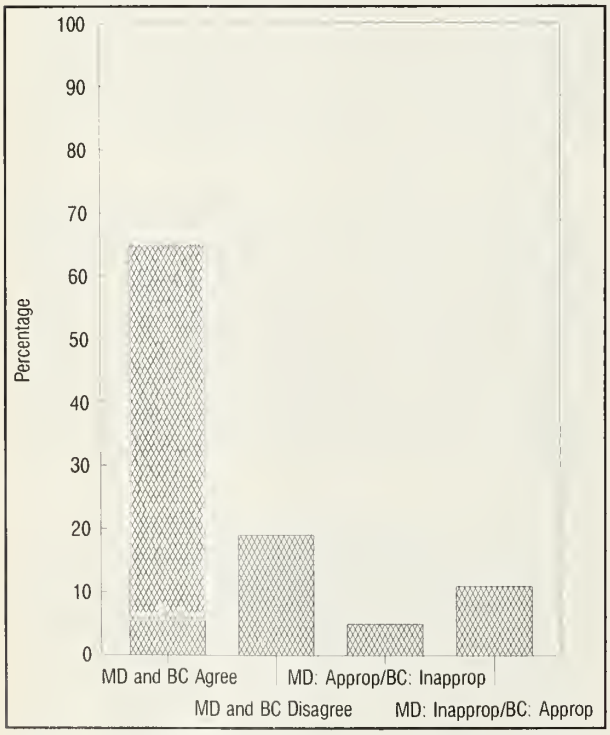

Figure 2.—Emergency department visits classified as appropriate (Approp) by physicians (MD) are compared with the appropriateness criteria of Buesching et al (BC) (K = .61).[3] Inapprop = inappropriate

Of the 132 visits determined by criteria to be inappropriate, the physicians thought that 43 (32.6%) were appropriate. Hereafter, if a visit was declared appropriate or inappropriate, its classification was determined by the criteria.

Table 2 shows the results of the multivariate logistic analysis of the effects of age, ethnicity, and primary payer on the occurrence of inappropriate visits.

Study variables were cross-tabulated with the appropriateness of the visit, and various subgroups were identified. As shown in Figures 3 and 4, there were significant differences in the percentages of inappropriate visits by age ($P < .0001$), ethnicity ($P < .002$), and primary payer ($P < .0001$), with the highest percentages of inappropriate visits occurring for ages 0 to 5 (47.3%), Hispanics (41.6%), and Medicaid recipients (48.8%). When ethnicity and primary payer are taken into account, the odds ratios for inappropriate use by young children compared with those by adults ages 20 to 39 are not significantly different from 1. Statistically significant increases occur in the odds ratios for Hispanics and Medicaid recipients, however.

In general, patients and physicians have differing opinions of how soon medical treatment is required (Table 3). Almost 90% of the patients felt that their condition required treatment in less than 12 hours, whereas physicians thought that only 66.5% of the visits required treat-

TABLE 2.—*Multivariate Analysis of Inappropriate Visits by Age, Ethnicity, and Primary Payer*

Variable	*Odds Ratio (95% confidence interval)**	*P value*
Age, years		
0-2	0.9 (0.4, 1.8)	.71
3-5	0.9 (0.4, 2.2)	.87
6-12	0.4 (0.2, 0.9)	.03
13-19	0.2 (0.1, 0.5)	.002
20-39	1.0	--
40-60	0.8 (0.4, 1.5)	.43
60+	0.2 (0.0, 0.5)	.002
Ethnicity		
Non-Hispanic white	1.0	--
Hispanic	1.9 (1.2, 3.0)	.008
African American	0.9 (0.2, 3.9)	.9
Primary payer		
Insurance	1.0	--
Self	0.8 (0.4, 1.7)	.62
Medicaid	2.2 (1.3, 4.0)	.005
Medicare	2.7 (0.9, 7.9)	.08

*Reference categories are as follows: Age 20-39, Non-Hispanic White, and Primary Payer—Insurance.

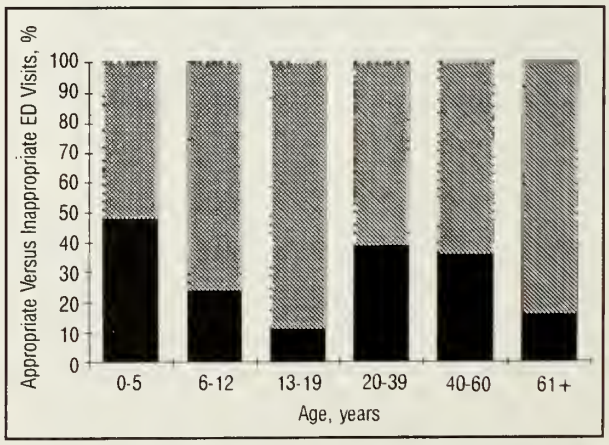

Figure 3.—The graphs depict the distribution of appropriate (▨) and inappropriate (■) emergency department (ED) visits by age.

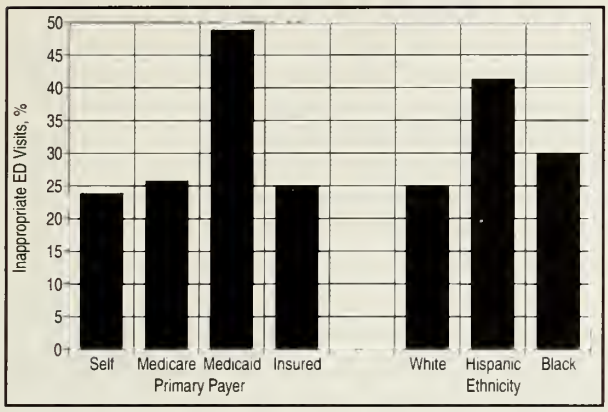

Figure 4.—The graphs depict the distribution of inappropriate emergency department (ED) visits by primary payer and ethnicity.

TABLE 3.—*Perceptions of Urgency*

Perception	%
Physician = patient	24.9
Physician > patient	33.3
Physician < patient	41.7

ment in that time period (Table 4). When a physician's perception of the need for treatment was matched with a patient's, a slight positive correlation ($r = .19$, $P < .0005$) was found. Patients and physicians agreed on the time frame for treatment in 26.6% of the cases. In 13.1%, the physician thought that care was needed sooner than the patient thought. In 184 visits (60.3%), the patient thought that treatment was required sooner than the physician did.

There was a significant correlation ($r = .51$, $P < .0001$) between the urgency of the condition and the need for treatment as perceived by the patient. Likewise, a significant correlation ($r = .72$, $P < .0001$) was found among the perceptions of the physicians. Patients and physicians both agreed that the more urgent the condition, the quicker treatment was required.

The top reasons a patient chose to come to the ED were as follows: the physician's office was closed (48%), the patient was able to get quick medical treatment (35.8%), the patient was too sick to wait for an appointment (31.3%), and the health problem had worsened (27.5%). Of the 326 visits with a completed patient questionnaire, only 7.5% of the patients said that they had no family physician.

Discussion

The definition of appropriate ED visit depends on whom you ask. As expected, patients and physicians have differing opinions. The medical literature fails to define appropriate use of the ED consistently. Thus, although numerous studies have attempted to quantitate the number of inappropriate visits,[3,4,6-8] the rate varies from 10.8% to 45% in urban settings.[3,7] The number of inappropriate ED visits in these studies was determined in several ways: by physician opinion,[6] by medical criteria,[7] and by the use of criteria that took into account the patient's perception in the decision to initiate the visit.[3,4]

The issue of defining the appropriateness of ED use is beyond the scope of this study. Therefore, it is limited by the lack of a standard measure of appropriateness. Limitations of the modified Buesching criteria include their failure to separate out children younger than 2 years with substantial fever. Most physicians would agree that a temperature of 38.5°C to 39.4°C in a child younger than 2 years is an appropriate reason to use an ED. Because modified Buesching criteria do not separate out these children, a temperature of below 39.4°C is considered an inappropriate use of the ED.

TABLE 4.—*Perceptions of How Soon Treatment Is Required*

	Immediately (within minutes),		*Urgently (1-2 hr),*		*Promptly (2-12 hr),*		*Delayed (> 12 hr),*	
Perceiver	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Patient	129	38.8	112	33.7	56	16.9	35	10.5
Physician	48	12.2	93	23.7	121	30.8	131	33.3

Nearly a third of the visits (32%) were found to be inappropriate as determined by criteria, and 24% were inappropriate based on physicians' opinion. This discrepancy may be due to the use of criteria specifying that if the duration of the chief symptom was greater than 48 hours, the visit was considered inappropriate. Numerous comments were made by the physicians that even though the visit was classified as appropriate at the time, it may have been inappropriate because of the duration of the symptoms.

The difference between the magnitude of correlation between physicians and patients may in part be explained by the method used to administer the survey. Patients completed the questionnaire before being seen by an attending physician. They may have thought survey answers had some bearing on being evaluated or receiving treatment. The physician questionnaire was completed after a patient was evaluated (retrospective). The fact that patients assessed the need to be seen before the medical evaluation whereas physicians reported appropriateness retrospectively makes the assessments more difficult to compare.

The application of criteria involves a substantial amount of judgment. To address this problem, only two of the authors were involved in applying the criteria. Also, the survey and study were discussed with the ED staff, both nurses and physicians, to try to standardize the administration of the questionnaires. This was easily accomplished because of the small size of the staff of the ED and the staff's cooperation.

Seasonal variation in ED use could be a bias of this study, but there was not substantial seasonal variation in the use of the ED. For 1992, the mean number of patients seen per day was 16.4, ranging from 14.7 in March to 18.1 in September. All other months ranged from 15.2 to 17.4 patients per day.

About 46% of the inappropriate visits were made by Medicaid recipients, who make up 15% of the general population of Roosevelt County. This number is less than that determined by Nelson and associates (64%).[4] Medicaid recipients constitute a large proportion of the inappropriate visits, which may be attributed to many factors. Because Medicaid is paying for the medical care, cost may not deter a visit to an emergency department.[9] Other possible explanations include that Medicaid recipients may perceive the ED as a good, quick place to receive medical treatment. Because emergency departments in rural areas may not be busy, the staff may be able to give them quick, friendly, and efficient care, even for a nonemergency. These reasons may also apply to many inappropriate visits by patients with other types of medical insurance coverage.[10]

The univariate analysis revealed high rates of inappropriate ED use in children aged 5 years and younger (33.3% of inappropriate visits). This age group accounts for 8.9% of the general population of Roosevelt County. Buesching and colleagues found that 21.4% of inappropriate visits were made by children in this group.[3] Patients at this age are susceptible to frequent infections that usually come on suddenly. A possible reason for this group's high rate of inappropriate visits may be that the parents are unsure what to do when their child becomes ill. Educating parents about daily care, such as quieting a crying child and managing a high temperature, may be beneficial in decreasing the number of inappropriate visits in this age group. Also, stressing to parents to phone the ED or a physician before making a visit could lower the rate of inappropriate visits.[11] Although this age group may have a higher rate of inappropriate ED visits, the multivariate analysis did not show an age of younger than 5 years as a significant factor when other factors were controlled for.

Identifying and characterizing the subgroups that frequently use the ED are important. By knowing which groups are more likely to have inappropriate visits, educational efforts can be directed more effectively. The financial solvency of a rural ED is an important factor in keeping the doors open for "true emergencies." The study did not analyze the possible effects of a reduction of inappropriate ED use. This type of analysis would be important to do before programs are created to reduce inappropriate ED use in a rural area.

Another subgroup identified in previous studies was those patients who did not have a personal physician. Even though only 7.5% of the patients in our study said they had no family physician, the low physician-to-person ratio may affect the ED use. Although there is only one nonfederal physician for every 3,400 persons in Roosevelt County,[12] the overall inappropriate use rate of 31.7% is similar to that in studies done in urban areas.

Finally, the study may be biased because of the missing data from questionnaires not completed by physicians or those not completed by patients. The demographic data available on these partial responses were not significantly different from those of patients with both the patient and physician questionnaires completed.

Conclusion

To decrease the frequency of inappropriate attendance, educational efforts should be focused on the subgroups with the highest rates of inappropriate use. In this study, Medicaid recipients would be a place to start. These frequent users[13] are candidates for intensive patient education, behavioral modification, and strengthened support from the health care systems.

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Conferences and Reviews

Ticlopidine Hydrochloride Use and Threatened Stroke

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Ticlopidine hydrochloride is an antiplatelet agent of proven antithrombotic efficacy that in December 1991 became available for general clinical use in the United States. The relative value of ticlopidine compared with aspirin, also an effective antiplatelet agent, has become a key clinical issue. Whereas ticlopidine is somewhat more effective than aspirin for preventing stroke in certain populations, it is also more expensive and potentially toxic. We recommend its use for patients with threatened stroke who are intolerant of aspirin and for patients who have cerebral ischemic symptoms despite aspirin therapy. Patients surviving major ischemic stroke make up a third group for whom ticlopidine use may be recommended in preference to aspirin. The use of ticlopidine rather than aspirin in patients with other cerebrovascular conditions is not strongly supported by existing data. The risk-benefit-cost equation involving ticlopidine versus other antithrombotic therapies is complex, rendering a wide range of acceptable management practices. If reliable laboratory monitoring for neutropenia during the first 3 months of therapy is not feasible, ticlopidine should not be used.

(Rothrock JF, Hart RG: Ticlopidine hydrochloride use and threatened stroke. West J Med 1994; 160:43-47)

Antiplatelet therapy reduces the risk of ischemic stroke in patients with many common types of cerebrovascular disease.[1] In December 1991, ticlopidine hydrochloride became available for general clinical use in the United States, with initial approval by the Food and Drug Administration restricted to the small fraction of patients with threatened stroke who are intolerant of aspirin therapy. Ticlopidine is an antiplatelet agent that is somewhat more effective than aspirin for preventing stroke, but it is also more toxic and more expensive. Should this agent be used more widely? Although recent reviews of ticlopidine therapy have addressed several aspects of this issue,[2,3] some confusion on the part of practicing clinicians yet exists. We assess the relative advantages and disadvantages of ticlopidine use over aspirin, and we propose a range of acceptable management practices for its use in patients with threatened stroke.

Ticlopidine Safety and Efficacy

Ticlopidine is an antithrombotic agent that has broad antiplatelet activity, is mechanistically distinct from aspirin and dipyridamole, and has the additional effects of reducing plasma fibrinogen levels and increasing erythrocyte deformability.[4,5] Many placebo-controlled, randomized clinical trials have established the efficacy of ticlopidine for preventing coronary artery bypass graft reocclusion,[6] death, and myocardial infarction in patients with unstable angina[7] or intermittent claudication,[8,9] progressive diabetic retinopathy,[10] and major stroke.[11] At a dose of 250 mg twice a day, ticlopidine is an effective antithrombotic agent.

Ticlopidine Versus Aspirin to Prevent Stroke

Aspirin is an effective, relatively safe, and fairly inexpensive antiplatelet agent. In doses varying from 75 mg to 1,300 mg daily, aspirin therapy reduces the risk of ischemic stroke following a transient ischemic attack (TIA) or minor stroke by 20% to 25%.[1,12,13] Even so, aspirin's effect on stroke incidence is relatively modest, and more effective antithrombotic agents are needed. To our knowledge, only two studies have addressed ticlopidine's effectiveness relative to aspirin for preventing stroke.[14,15] One of these, from Japan, was reviewed only briefly in the English-language literature, and its results consequently are difficult to assess critically.[14] The other was the Ticlopidine versus Aspirin Stroke Study (TASS).[15]

This study compared the use of aspirin, 650 mg twice a day, and ticlopidine, 250 mg twice a day, in 3,069 randomly assigned patients with a TIA or minor ischemic stroke.[15] The three-year event rate for nonfatal stroke or death from any cause (the primary end-point analysis) was 17% for ticlopidine and 19% for aspirin, a 12% relative risk reduction for ticlopidine compared with aspirin by intention-to-treat analysis ($P = .05$). The rates of fatal and nonfatal stroke at three years were 10% for ticlopidine and 13% for aspirin, a 21% relative risk reduction for ticlopidine ($P = .02$; Table 1). Hence, ticlopidine was superior to aspirin for preventing stroke in at-risk patients in

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ABBREVIATIONS USED IN TEXT

TASS = Ticlopidine versus Aspirin Stroke Study
TIA = transient ischemic attack

this well-executed, double-blind clinical trial, and the difference was statistically significant.

Are these results valid, clinically important, and thus applicable to general practice? A closer inspection of the TASS patient population suggests possible selection bias weighing against patients who took aspirin. Many patients enrolled in TASS were receiving aspirin at the time of their qualifying event, and these "aspirin failures" were then randomly assigned to receive aspirin or ticlopidine. A secondary analysis of the TASS data showed that previous antithrombotic therapy was predictive of a poorer response to aspirin during the follow-up period—that is, aspirin failures remained aspirin failures (Table 2).[16] The relative efficacy of ticlopidine versus aspirin for preventing stroke in patients not previously treated with aspirin is therefore uncertain.

In assessing the clinical importance of a therapy, the relative risk reduction may not be as useful a measurement as the absolute risk reduction conveyed by that therapy. Based on the TASS results, ticlopidine use should reduce the absolute risk of stroke by about 1% per year relative to aspirin during three years of therapy. Table 3 illustrates the cost-to-benefit ratio of ticlopidine versus aspirin versus no therapy for 100 hypothetical patients with a TIA or minor stroke. Applying these data to an estimated 500,000 Americans who will suffer a TIA or minor stroke within the next 12 months leads to the conclusion that the routine use of ticlopidine rather than aspirin in that population would reduce the incidence of subsequent stroke by an additional 15,000 cases over the ensuing three years. At an additional $2,260 dollars per patient treated, such standardized intervention would cost $1.13 billion more with ticlopidine than with aspirin.

No study has yet compared ticlopidine and aspirin therapy directly for secondary stroke prevention following *major* stroke. In the Canadian-American Ticlopidine Study, ticlopidine was demonstrably superior to placebo for this indication.[11] Its wide use notwithstanding, aspirin has not been tested thoroughly and specifically for secondary stroke prevention in patients with disabling ischemic stroke, but it is likely to be of benefit.[17]

TABLE 1.—*Results of the Ticlopidine versus Aspirin Stroke Study*

Results of Treatment	Treatment Assigned: Ticlopidine (n=1,529)	Treatment Assigned: Aspirin (n=1,540)	Difference	Relative Risk Reduction, %*
Ischemic strokes	169	208	−39	−19
All myocardial infarctions	104	89	+15	+17
All vascular deaths	120	116	+4	+3
Nonvascular deaths	44	67	−23	−34
All deaths	164	183	−19	−10
All deaths or strokes	306	349	−43	−12

*Risk reductions and *P* values cited in text are based on Kaplan-Meier ratios and thus differ slightly from the figures presented here.

TABLE 2.—*Use of Ticlopidine Hydrochloride for Aspirin Failure**

Prior Aspirin Use	Patients, No.†	Treatment Assigned, No.: Ticlopidine HCl	Treatment Assigned, No.: Aspirin	Stroke Incidence, %: Ticlopidine HCl	Stroke Incidence, %: Aspirin
Yes	2,570	1,273	1,297	7.5	11.9
No	464	242	222	6.6	4.9

HCl = hydrochloride

*Data are derived from the Ticlopidine versus Aspirin Stroke Study (TASS). From Hass et al.[15]
†"It can be presumed that patients previously treated with anticoagulants or platelet antiaggregant drugs primarily had received aspirin, and that continued treatment with aspirin was less effective than ticlopidine" (Grotta et al[16(p114)]).

Ticlopidine Versus Aspirin to Prevent Myocardial Infarction and Vascular Death in Patients With Cerebrovascular Disease

In assessing optimal antithrombotic therapy for patients who suffer stroke or TIA, the effects of therapy on the incidences of myocardial infarction and vascular death must also be considered. The data from TASS indicate that ticlopidine has no advantage over aspirin for preventing myocardial infarction or vascular death in patients with a TIA or minor stroke (Table 1). Inexplicably, the major effect of ticlopidine on mortality relative to aspirin involved nonvascular deaths. When the constellation of major vascular events (all ischemic strokes, myocardial infarctions, and vascular deaths) is considered, the TASS results demonstrate only a slight advantage for ticlopidine over aspirin (estimated intention-to-treat results: 345 events on ticlopidine therapy versus 357 events on aspirin therapy; 3% relative risk reduction).[17]

Ticlopidine therapy is associated with a mean 9% increase in total serum cholesterol.[8,15,18] Given the relatively short follow-up period in existing clinical trials, any adverse clinical consequences of this increase may not have been fully manifested. In the clinical trial with the longest follow-up period,[8] myocardial infarction occurred in 20% of placebo-assigned patients versus 17% of ticlopidine-assigned patients (a 12% relative risk reduction), but it is impossible to correct for the competing influences of antiplatelet effect and cholesterol elevation.

In summary, ticlopidine's benefit in patients with TIA and minor stroke appears to be confined to preventing ischemic stroke, and this involves an absolute reduction of about 1% per year relative to aspirin.

Subgroup Analysis

Although considerable controversy exists concerning aspirin's efficacy in women, recent data and aggregate meta-analysis of the large antiplatelet trials do not suggest a differential effect for aspirin according to gender.[12,19] Even so, the Food and Drug Administration has not approved aspirin use for preventing stroke in women with TIA or previous stroke. Ticlopidine's clear efficacy in women may provide some justification for its wider clinical use. In TASS, ticlopidine reduced the stroke incidence in women by 27% relative to aspirin (intention-to-treat analysis), but the lower incidence of stroke recorded in

TABLE 3.—*Estimated 3-Year Stroke Rates and Costs of Therapy in 100 Patients With Transient Ischemic Attack or Minor Stroke*

Therapy	*Strokes, No.**	*Cost per Patient, $*	*Cost per Stroke Prevented, $*
No therapy	16	0	NA
Aspirin	13	50	1,667
Ticlopidine HCl	10	2,310†	38,500

HCl = hydrochloride, NA = not applicable

*Event rate estimates are based on data from the Ticlopidine versus Aspirin Stroke Study and meta-analysis of aspirin studies (from Antiplatelets Trialists' Collaboration[12] and Hass et al[15]).
†Includes cost of 6 complete blood counts for each patient during the first 3 months of ticlopidine therapy.

women compared with men reduces the clinical importance of this seemingly impressive risk reduction. Subsequent "on treatment" subgroup analysis revealed ticlopidine to have been almost twice as effective as aspirin in reducing the three-year cumulative stroke risk in women (5.2% versus 10% in men).[16]

Additional subgroup analyses of TASS data have suggested a differential effect for aspirin relative to ticlopidine in patients with diabetes or hypertension, vertebrobasilar symptoms, or major carotid stenosis.[16] Such data should be received with skepticism pending confirmation from prospective, well-controlled clinical trials.

Ticlopidine Plus Aspirin

The combination of ticlopidine and aspirin has not been studied sufficiently to establish the safety and advantages of this therapy over monotherapy. As results from in vitro platelet function testing and from the observed prolongation of bleeding times indicate, the antiplatelet effects of this combination appear to be additive.[20,21] Whether these additive effects would be valuable clinically or would produce undue bleeding, particularly brain hemorrhage, or other toxicity is unknown. At present, the use of ticlopidine with aspirin or another nonsteroidal anti-inflammatory drug is not recommended.

Safety

Except for a 1% incidence of severe neutropenia and a similarly low incidence of thrombocytopenia, the side effects of ticlopidine are minor. Ticlopidine-associated neutropenia typically occurs during the first three months of therapy, and complete blood counts every two weeks consequently are recommended during that period. In all reported cases, neutropenia has resolved after the withdrawal of ticlopidine. The frequency with which neutropenia and its associated morbidity occur in clinical practice will be a key factor in determining whether ticlopidine use gains widespread acceptance.

Cases of thrombocytopenia, thrombotic thrombocytopenia purpura, and even pancytopenia complicating ticlopidine therapy have been reported.[4,22-26] Such complications have tended to occur within the initial weeks of treatment. Consequently it is recommended that ticlopidine-associated hematologic monitoring include a platelet count.

Diarrhea, occurring in about 10% of patients, and rash, occurring in about 5%, are more frequent but less serious side effects of ticlopidine. Gastrointestinal intolerance appears to occur more commonly with high doses—more than 1,000 mg daily—of aspirin than of ticlopidine.

Cerebrovascular Indications for Ticlopidine Therapy

The advantages and disadvantages of ticlopidine therapy for stroke prevention are outlined in Table 4. Several points should be emphasized before considering ticlopidine's possible role in specific clinical settings. First, stroke is often a devastating and dehumanizing illness; although weighing economic considerations against such an illness is a task most physicians would prefer to avoid, it is a reality we cannot afford to ignore. Second, clinical data often suggest trends that, although not statistically significant, are nonetheless compelling. A lack of proven efficacy does not necessarily imply inefficacy. In instances where clinical trials have not been done to address specific issues, one is tempted to extrapolate from results obtained in similar, but not identical, clinical settings. Given these uncertainties and the changing nature of clinical research, there is room for clinical scientists to disagree, and a range of acceptable management practices, rather than dogmatic recommendations, seems warranted in most situations. Finally, the safety of ticlopidine may not be the same in general clinical practice as it was in the randomized clinical trials, where patients were selected for compliance and observed according to strict protocols.

Prevention of Stroke in Aspirin-Intolerant Patients With Noncardioembolic TIA or Previous Stroke

The efficacy of ticlopidine has been established more solidly than that of any alternative antithrombotic agent. Therefore, ticlopidine should be considered the antithrombotic therapy of choice in the setting of aspirin intolerance. Even so, aspirin intolerance is often dose-related; patients unable to tolerate at least 325 mg of aspirin per day are uncommon, and yet lower doses of aspirin may be effective for preventing stroke and inducing fewer side effects.[13] If a patient cannot tolerate 325 mg or more of aspirin per day, then a reasonable alternative is to prescribe either ticlopidine or aspirin at a lower dose.

TABLE 4.—*Use of Ticlopidine Hydrochloride in Threatened Stroke Compared With Aspirin*

Advantages of Ticlopidine	Disadvantages of Ticlopidine
20% Relative reduction in stroke incidence; 1% per year absolute stroke risk reduction*	Expense—± $900 in 1st year
Clearly effective in women	Requires bimonthly complete blood counts for 3 months
Proved effective (compared with placebo) in survivors of major ischemic stroke	1% Risk of reversible neutropenia
	Mild (10%) elevation of all cholesterol fractions†

*Relative to aspirin, 1,300 mg daily.
†Clinical significance uncertain.

TABLE 5.—*Recommended Antiplatelet Therapy for Patients With Noncardioembolic Ischemic TIA and Stroke**

Patient History	*Recommendation*	*Reasonable Options*
TIA or minor stroke†	Aspirin, 325 mg/d	Aspirin, 75-1,300 mg/d Ticlopidine HCl
TIA or stroke on aspirin therapy	Ticlopidine HCl	Continue aspirin, possibly increase dose Warfarin INR 2 to 3 for 3 to 12 mo‡
Major stroke	Ticlopidine HCl or aspirin	Ticlopidine or aspirin Warfarin INR 2 to 3 for 3 to 12 mo‡

HCl = hydrochloride, INR = international normalized ratio, TIA = transient ischemic attack

*These recommendations do not apply necessarily to patients with symptomatic—TIA or minor stroke—carotid stenosis of 70% or more. Data from the North American Symptomatic Carotid Endarterectomy Trial indicate that carotid endarterectomy is superior to best medical therapy for such patients (from North American Symptomatic Carotid Endarterectomy Trial Collaborators[12]).

†Women at high risk for recurrence may represent a special subpopulation in whom ticlopidine particularly should be considered as initial therapy (from Swedish Aspirin Low-Dose Trial[13]). Given available data, however, we think that aspirin is the most reasonable initial therapy.

‡Given the absence of data indicating the efficacy of such treatment and the likelihood that warfarin will convey a substantially higher risk of hemorrhagic complications than a therapy of proven benefit, such as ticlopidine, this option must be considered to fall just within the boundaries of the range of acceptable management.

Prevention of Stroke in Patients Experiencing TIA or Stroke During Aspirin Therapy

No compelling data suggest that altering the dose of aspirin or adding another antiplatelet agent, such as dipyridamole, is useful therapy when aspirin therapy fails, and the role of anticoagulant therapy has not been established. The current range of acceptable management practices, however, includes continuing aspirin therapy at the existing dose, increasing the aspirin dose to a maximum of 1,300 mg daily, using short-term anticoagulation therapy, or ceasing aspirin therapy in favor of ticlopidine (Table 5).[27] Given the TASS data outlined earlier, we regard the last as the treatment of choice. With the availability of ticlopidine, the empiric use of warfarin in this setting is particularly difficult to justify, especially given the increased expense and risk associated with that agent. Aspirin failure is the most common indication for ticlopidine use in our practices.

Primary or Secondary Prevention of Cardioembolic Stroke

Because aspirin and warfarin both have established efficacy in selected patients at risk for cardioembolic stroke and ticlopidine's usefulness in this setting has not been assessed, ticlopidine should not be used instead of these agents to prevent cardioembolic stroke.[1]

Initial Antithrombotic Therapy for TIA or Minor Ischemic Stroke

Should ticlopidine therapy ever be tried before aspirin therapy in patients with TIA or minor stroke? The routine use of ticlopidine in this setting would result in a relatively modest reduction in stroke incidence at considerably increased expense (Table 3). This high cost-benefit ratio combines with the risk of severe neutropenia; the lack of documented benefit over aspirin interrupting the progression from stroke to myocardial infarction to vascular death; persisting doubt as to ticlopidine's superiority to aspirin in patients for whom aspirin therapy has not yet failed; and the mild elevation in serum cholesterol, albeit of uncertain clinical significance, to dampen our enthusiasm for routine intervention with ticlopidine. Whereas aspirin should remain the initial antithrombotic agent of choice in this setting, ticlopidine represents an acceptable alternative therapy for patients willing to obtain the required hematologic monitoring. If ticlopidine is selected as the initial therapy, its use should be reserved in particular for women with hypertension, diabetes mellitus, or both.[16]

Initial Antithrombotic Therapy Following Major Noncardioembolic Stroke

Compared with placebo, ticlopidine has been shown to be effective for the secondary prevention of stroke and other vascular events in patients with previous stroke that has resulted in a substantial residual neurologic deficit.[11] The efficacy of aspirin therapy in these patients is less well established,[1] but there is no compelling reason to believe that the severity of neurologic residua is an important determinant of aspirin efficacy. Favoring ticlopidine is a higher risk of recurrent stroke in patients with major stroke, relative to those with a TIA or minor stroke, and thus a more appealing cost-benefit profile.[28] Although aspirin remains an acceptable alternative therapy in this setting—indeed, the only reasonable alternative at this point—our first choice for patients who have suffered a disabling noncardioembolic major stroke despite aspirin therapy is ticlopidine. In addition, ticlopidine therapy can be considered for those patients with major stroke who have not taken aspirin.

Conclusion

Ticlopidine is an effective antithrombotic agent, and its availability expands our therapeutic options and represents an advance in the treatment of threatened stroke. Although ticlopidine may be superior to aspirin in certain clinical settings, it carries the burdens of higher expense and infrequent but severe neutropenia. Given currently available data, ticlopidine can be considered optimal therapy for preventing stroke in the following situations: recent TIA or stroke in aspirin-intolerant patients, recent TIA or stroke despite concomitant aspirin therapy, and possibly recent major stroke, regardless of whether this occurred during aspirin therapy. In the last two situations, however, aspirin represents acceptable alternative therapy. If close monitoring for neutropenia cannot be done reliably during the first three months of ticlopidine therapy, that agent should not be used.

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Conferences and Reviews

Performing Arts Medicine

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Arts medicine has come of age, resulting from 3 important developments over the past decade: improved methods of diagnosis and treatment, an awareness that artists suffer from special problems related to their occupation and lifestyle, and the establishment of health programs emphasizing an interdisciplinary approach to these patients. We focus on the patterns of illness afflicting performing artists, specifically dancers, singers, actors, and instrumental musicians, and explain some of the things a health care team can do in treating these patients. The conditions governing these patients' lives—early exposure to high expectations of excellence, incessant demands for perfection, long periods of intense practicing, fierce competition, high levels of anxiety associated with performance, and uncertain careers—need to be understood. Levels of disease and disability are remarkably high, but artists often ignore symptoms. We discuss the musculoskeletal, neurologic, vocal, psychological, and other syndromes found among performers and some of the difficulties in treating them. The prevention of injury, conservative management, collaboration with teachers, and a psychotherapeutic approach are desirable. Arts medicine programs for professional consultation exist in several major cities of the United States and abroad. Although research is needed regarding the effectiveness of health care services for performing artists, the scientific literature devoted to this field is growing.

(Ostwald PF, Baron BC, Byl NM, Wilson FR: Performing arts medicine. West J Med 1994; 160:48-52)

Performing artists face injuries and illnesses that stem from years of intensive training and the demand for peak functioning in the public eye. A 22-year-old violinist giving a concert debut will have studied more than 15,000 hours to perfect motor skills and musical understanding. Ballet dancers attend classes as young children to develop the strength and precise coordination needed to dance with the style and grace expected of them. According to a recent survey of American orchestral musicians, 82% experienced medical problems, with 76% reporting at least one problem severe enough to interfere with performance.[1] Among dancers the rate of serious injury, sampled over a period of eight months in one study, was 97%.[2]

The first treatise on disability in performing artists appeared in 1713, but only in the past decade have specialized medical programs for performing artists been organized.[3] Although a growing number of physicians, surgeons, and allied health professionals are becoming interested in the causes and care of performers' disorders, most lack experience in this area.[4] Millions of Americans participate in performing arts. This includes students, amateurs, apprentices, teachers, coaches, part-time artists, and 200,000 professional performers. Clearly the number of skilled medical practitioners is inadequate to care for this population.

Each type of performing artist will have slightly different problems, depending on the system most taxed—vocal cords in a singer; hips, backs, knees, and ankles of a dancer; and fingers, wrists, elbows, shoulders, and neck of a string player or pianist. Beyond this are general stresses related to having to perform under conditions of high adrenaline flow, anxiety, fatigue, social pressure, and financial insecurity. We review the problems commonly seen in dancers, vocal artists, actors, and instrumental musicians.*

Problems of Dancers

Foot injuries occur often in ballet dancers. Toe dancing *(sur les pointes)*, the expected form for women, results in nonphysiologic weight bearing that exaggerates the metatarsal arch and can lead to distorted posture.[5] This may produce fatigue, pain, stiffness of the tarsal joints, hallux valgus, bunions, and hammertoes. Excess loading of the foot joints can cause early arthritic changes, with bony spurs, narrowing of the joint spaces, and restricted motion. These create pain and, with efforts to relieve it by shifting weight, the potential for further injury. Treatment of acute foot discomfort consists of elevation and active motion to reduce edema and stiffness; padding of the dance shoes and molded arch supports may serve as preventive measures. In some cases surgical intervention is

*See also the editorial by R. J. Lederman, MD, "The Coming of Age of Performing Arts Medicine," on pages 73-74.

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needed, but arthrodesis should be avoided because it risks reducing the range of motion in a dancer's foot.

Microfractures of bones in the foot and ankle resulting from repeated impact with hard unyielding surfaces frequently go unnoticed in the early stages and fail to heal properly. Tenderness may be either diffuse or pinpoint, followed in several weeks by the sudden sharp pain of a "stress fracture," invisible on x-ray film. Even bone scans and computed tomographic scans have been known to be normal for the first few weeks. Treatment includes rest, ice packs, bandages, splints, and crutches to reduce weight bearing. If spontaneous repair does not occur, a bone graft may be indicated.[6]

Other disabling conditions include muscle spasm, ligamentous strain, tendinitis, nerve damage, injuries of the back, hip, or knee, and various cysts and dislocations. Modern dancers suffer mainly from back and knee problems, whereas classical ballet dancers more often have foot and ankle injuries.[7] Dislocation of the patella is relatively common in dancers. Typically a twisting injury is followed by severe pain, immediate swelling (due to hemarthrosis), and a distorted appearance. By the time a physician is consulted, the knee is so swollen that the diagnosis may be missed unless x-ray films are taken.[8]

Delayed menarche occurs in 70% of female dancers, with secondary amenorrhea seen in 50% of adolescent and 78% of adult dancers.[9] These problems frequently are linked to eating disturbances.[10] Female dancers strive to maintain a slender figure and low weight. A study of midteen student ballerinas showed that 25.7% met criteria for anorexia nervosa and 14.2% had bulimic syndromes.[11]

Enforced early retirement further complicates a dancer's career, which usually peaks in the late teens and early 20s. With declining strength and cumulative injuries, many are no longer in demand as performers by the time they reach their mid-30s. A few stay on as character dancers, coaches, teachers, or choreographers, but most dancers approach retirement in great emotional turmoil.[12]

Physicians treating dancers must be familiar with the artistic and social conditions governing their lives. Attending to their psychological difficulties, focusing on prevention (including conditioning, stabilization, and muscle rebalancing), the early diagnosis of injury, conservative management, and restoring functional ability are essential in the practice of dance medicine.

Problems of Vocal Artists and Actors

Simple ailments can disproportionately affect performance in singers and actors. Upper respiratory tract infections or acute allergic illnesses may interfere minimally with a nonperformer's life but can greatly change or prevent a singer's performance. Failure to understand this often leads physicians to label an artist-patient as "hyper" or "difficult." If the patient is a singer or actor, common maladies such as eustachian tube dysfunction after flying, otitis media with effusion, sinusitis, allergic rhinitis, laryngopharyngitis, and bronchitis require quick diagnosis and the immediate initiation of treatment. Taking blood specimens for culture and other blood tests is worthwhile, but the physician should not wait for the results to begin treatment. When performers have concerts or auditions in 24 or 48 hours, a "wait-and-see" approach increases the level of anxiety and results in delayed treatment and possibly a cancelled performance and damaged career. For the disorders mentioned earlier, amoxicillin with clavulanate potassium or a cephalosporin such as cefuroxime are appropriate choices.

Physicians should caution singers and actors to avoid frequent coughing and throat clearing, both of which lead to laryngeal edema and hoarseness. For most upper respiratory tract and laryngeal problems, performers are helped by a mucolytic such as guaifenesin, increased oral intake of fluids, and the use of a vaporizer in the bedroom at night. These measures thin tenacious mucus that can interfere with good vocal technique. Antihistamines are drying and remove natural lubrication; they should be taken only after a performance.

After completing the history, examine the patient, making certain to view the vocal cords thoroughly. Commonly encountered noninfectious problems include edema, nodules, and hemorrhages due to voice abuse, reflux laryngitis, and hormonal abnormalities. Saying that the cords are free of disease reduces anxiety, but positive findings tend to have the opposite effect. The treatment of vocal nodules involves work with a speech therapist and a temporary reduced use of the voice. Most nodules resolve without the need for surgical excision.

Experienced performers often know the symptoms of a recurrent ailment and request medication that has helped in the past. Reasonable requests should be honored, but the demand for an oral steroid may signal a habitual problem that will lead to further problems. Steroids are indicated for swelling of the vocal cords severe enough to ruin an audition or concert. They should be used on an infrequent and selective basis only by physicians experienced in treating performers.

Reflux laryngitis caused by gastric acid regurgitation sometimes develops in professional singers. Substernal burning with an acid taste when lying down, pain on vocalizing, and the finding of erythematous arytenoid mucosa are keys to the diagnosis. Treatment involves elevating the head of the bed, avoiding late evening meals, and taking antacids. Premenstrual hormonal changes may result in fluid retention in the vocal cords and hoarseness. If thyroid abnormalities are the suspected source of vocal dysfunction, a full medical evaluation is required.[13]

Disorders of Instrumental Musicians

Skin Problems

Skin disorders in musicians vary widely, depending on the instrument played and the material it is made from. Lesions appear at the point of contact (in the mouth, on the lips, under the chin, between the legs), based in part on whether the instrument offers support (an organ or piano) or has to be supported (a trombone or guitar). Left-sided submandibular lesions develop in 62% of violinists and violists from holding their instrument.[14]

Seemingly minor ailments such as bruises, calluses,

cuts, abrasions, ulcers, eczema (allergy to bow resin), and hyperhidrosis can interfere substantially with practicing and performing.[15] A recent survey found work-related skin problems among 32% of the string players and 27% of the wind and brass players questioned, compared with 9% of nonmusician controls.[16] Consultation with a dermatologist is usually indicated.

Musculoskeletal Injuries

Various musculoskeletal problems can result from the repetitive movements required of instrumentalists. Aching, burning, fullness, tiredness, or pain in one or more body parts involved in playing the instrument are usually the initial symptoms. These problems commonly develop after an unusually intense or prolonged period of practicing and performing, often of difficult repertoire, sometimes on a different or unfamiliar instrument. Later, symptoms occur even with playing for short periods. Contributing factors may include tension or excessive finger articulation, fatigue, poor posture, physical disproportions between the player's anatomy and the instrument, and adverse biomechanical preconditions in the hand, such as hypermobility or hypomobility of critical joints.[17] Among string players, women appear to be more vulnerable than men to severe musculoskeletal problems.[18]

Overuse disorder or cumulative trauma disorder, often diagnosed in occupational medicine, is being identified with increasing frequency in musicians.[19] This diagnosis implies that tissues of the body have been stressed beyond their limits. Clinical evaluation requires considerable time and patience, and it is essential to examine musicians with their instruments to observe posture, signs of tension, disproportions between player and instrument, range of motion, and the position of wrists, elbows, shoulders, neck, and back. How the fingers move should also be noted, particularly if there are difficult reaches or if the musician aggressively uses the finger extensors and flexors rather than the intrinsic muscles of the hands to create pressure, which can then be simply released instead of having to extend against gravity.

Management is summarized in Table 1. An immediate reduction of playing time is desirable to allow healing, but performers may resist this because of having to meet concert schedules. Heat and soft tissue mobilization before play, cold applications with the stressed limb in a stretched position after performance, and analgesic or nonsteroidal anti-inflammatory drugs are helpful. With sufficient rest and appropriate exercises to balance intrinsic with extrinsic muscles, restore normal synergies, and release adhesions, the symptoms usually subside within a few weeks. If neglected, overuse syndromes may escalate until there is persistent and severe pain, even when not playing the instrument, requiring much longer time for recovery and increasing the risk of prolonged disability.[20]

To avoid career complications and to minimize the risk of injury during playing, it is advisable to involve a patient's teacher, coach, or manager in making plans for treatment and rehabilitation. For ergonomic reasons, it may also be helpful to suggest physically altering a musical instrument, such as changing the position of keys on a clarinet or flute, modifying the chin and shoulder pads of a violin or viola, or using straps and supports to reduce the weight of heavy brass and woodwind instruments.[21] Unless they are experienced musicians themselves or working closely with music teachers, examining physicians should avoid suggesting substantial changes in playing techniques.

TABLE 1.—*Management of Musculoskeletal Injuries in Musicians*

Reduce playing time
Warm up before playing
Incorporate periods of rest into sessions that make excessive demands on structure
Correct problems of performing technique
Reduce static and dynamic loads
Allow the choreography of the instrument to adapt to the hand
Use nonsteroidal anti-inflammatory drugs
Physical or occupational therapy—splints, ice, exercise, adaptive devices
Ultrasonography, soft-tissue and neural mobilization, sensory and motor re-education
Relaxation training, Alexander technique, Feldenkrais method
Local injections
Surgery
Counseling; psychotherapy
Balanced diet, adequate hydration

Neurologic Complications

Nerve entrapment and focal dystonia. Loss of sensation and eventual interference with motor control result from a variety of conditions that put pressure on adjacent nerves. These include hypertrophy of muscles and tendons, playing postures that require prolonged positioning with the joints at end ranges, as well as fat and fluid accumulation in narrow spaces at the wrist (carpal tunnel syndrome), elbow (cubital tunnel syndrome), and thoracic outlet.[22] In addition to a complete neurologic examination, it is essential to carry out specific clinical tests, such as checking the warmth of the hands, the symmetry of arterial pulsation, strength, size, and coordination of muscles, and sensory abilities. Auscultation at the site of suspected entrapment may reveal friction noise. If electromyographic and nerve conduction studies are done, patients should practice their instrument for at least an hour before testing. With magnetic resonance imaging, the affected area should be visualized in both neutral and playing positions because compression may occur only when the patient is playing.

Although surgical decompression has dramatically benefited some performers, extreme caution is required. Frequently patients have problems at multiple levels. The first approach should be conservative—the release of soft tissue restrictions around the area plus improved posture and modification of playing positions. If surgical treatment eventually seems necessary, a hand specialist experienced in treating musicians and familiar with the special risks involved should be consulted.[23]

Focal dystonia (also called "cramp") is a disorder that can have devastating consequences for musicians.[24] There

is interference with the speed, coordination, and accuracy of movements controlling the instrument. In pianists the fourth and fifth digits curl uncontrollably into the palm of the hand and the index finger extends excessively. Trumpeters lose control over fine adjustments of the lips and tongue; string instrumentalists can no longer finger their notes accurately. Initially these symptoms are task specific and usually disappear when patients are not playing their instrument, pointing to possible psychogenic factors. Identifying subtle nerve entrapments, biomechanical abnormalities, anteceding trauma, and characteristic training patterns leads to a clearer understanding of cause. Research with nonhuman primates suggests that changes in the sensorimotor cortex occur with repetitive performance.[25]

Treatment with various methods of sensory and motor retraining, psychotherapy, pharmacotherapy, and local injection of botulinum toxin has generally yielded less than satisfactory results. Early intervention to change habits that may trigger abnormal movements appears critical. A few patients have recovered after prolonged retraining with new music and different techniques, but further research is needed to pinpoint the cause of focal dystonia.[26]

Arthritis

Although many instrumentalists continue to play despite arthritis, degenerative change in the bones of the wrist and fingers can be progressively disabling. This is especially the case if the range of motion of the carpometacarpal joint of the thumb or the interphalangeal joints of the fingers are restricted or if there is considerable pain with performance. Responding promptly to tendinitis or fasciitis as harbingers of abuse or excessive use may prevent some arthritis. Exercise has a beneficial effect on repair, collagen deposition, and tendon strength, whereas immobilization or excessive rest brings about unnecessary demineralization of bones and atrophy of muscles. Taking the time to change playing techniques before damage results is critical to long-term health. This requires having the patient try to play or perform with the joints in midrange, with more careful use and balance between the muscle stabilizers and movers under conditions of good circulation. Playing in a well-heated environment, warming the extremities, and increasing general body metabolism under conditions of good hydration help to maintain perfusion and oxygenation of tissues.[27]

Although rheumatoid arthritis is no more common among performing artists than among others, it is definitely associated with deformities that are usually incompatible with continued high-level performance.

Other Conditions

Repeated intense pressure within the pharynx of wind instrument players—brasses and woodwinds—can produce dilatation and outpouching, and several cases of pneumothorax have been reported.[28] Periodontal disease, malocclusion, loose or missing teeth, and other dental problems may seriously affect performance, requiring the design of special dentures.[29] Loss of muscular strength and coordination between lips and tongue, temporomandibular joint dysfunction, facial pain, and other oropharyngeal disorders need to be evaluated and treated to preserve a wind player's career.[30]

With the increasing size of orchestras, loudness of instruments, and especially the introduction of electronic amplification, the incidence of hearing disturbances has grown among musicians. Rock and roll musicians were first thought to be at greatest risk, but symphony players' daily exposure to high-intensity sound at rehearsals and concerts makes them equally vulnerable. Because of the obvious importance of good hearing for musicians, deficits and their possible causes—trauma, infection, nerve damage, aging—should be evaluated by otologic and audiometric examination and promptly treated.[31] Measures to prevent hearing loss include education, the avoidance of excess noise exposure, shields to deflect the sound of high-intensity instruments, and the use of earplugs designed to reduce sound levels without interrupting feedback.[32]

Psychological and Emotional Issues

Success in the performing arts demands an almost exclusive focus of time and intellectual and emotional energy. Having sacrificed, in many cases, typical social experiences during childhood and adolescence in favor of career advancement, professional artists may have fewer skills in coping with stress. Performers who fail to meet their own goals or to win acceptance from others sometimes suffer from psychological symptoms that call for treatment both in their own right and because they hinder ongoing medical therapy.[33]

Depression among performers can occur when there is a loss of opportunity, popularity, self-esteem, or physical integrity due to illness, injury, and aging. The contrast between postperformance highs and the mundane pressures of daily life raises the likelihood of acute depression in susceptible persons.[34] Sensitive to their reputations, performers may attempt to disguise or deny depression or other unacceptable emotions.

Anxiety surrounding important auditions and concerts is extremely common.[35] Mental symptoms include pronounced apprehension, a dread of failure, and fears of memory lapses, losing control, and being disgraced. Often observed physical symptoms are muscle tension, tremulousness, respiratory distress, palpitations, dry mouth and throat, loss of sphincter control, and other hyperadrenergic responses. Many artists develop personal coping stratagems. Some use self-hypnosis, relaxation exercises, or deep breathing. Others who insist that stage fright adds to the excitement of performing need not be treated, but some are so disturbed by it that they retreat from public exposure. Physicians need also to stay alert to the destructive role of self-medication with drugs and alcohol.

The management of psychological problems among performing artists demands sufficient time for these patients to relax, establish trust, and lower their defenses. In contrast to the 10- to 15-minute contacts (about which patients often complain)[36] dictated by physicians' busy schedules, consultations lasting 60 to 90 minutes seem more

successful. Artists will often want to know how the therapist feels about their performances and whether they have attended concerts or read reviews. Although it is desirable to show interest in what a performer does, extreme enthusiasm or criticism may lead patients to see the therapist as yet another parent, teacher, or agent more interested in their fame than in aspects of their health.

Psychoactive medications must be used judiciously with artists, keeping in mind that certain side effects—drowsiness, dry mouth, insomnia, tremor—may interfere with high-level performance. Nonsedating antidepressants, such as nortriptyline hydrochloride and sertraline hydrochloride, have proved to be effective in treating musicians and dancers who are depressed. For the treatment of performance anxiety, the use of β-blockers such as propranolol hydrochloride, taken in low doses (10 to 20 mg) an hour before going on stage, has become popular. Anxiolytics, such as alprazolam and diazepam, are recommended for treating the generalized anxiety syndromes of performing artists, and monoamine oxidase inhibitors such as phenelzine sulfate are useful when severe anxiety (panic) and depression coexist.

Conclusion

No single physician, surgeon, psychiatrist, or other health professional, regardless of the scope of his or her skills, can treat the vast range of problems and disabilities occurring among performing artists. That is why recently organized programs in Boston, Chicago, Cleveland, San Francisco, New York, Washington, DC, and other metropolitan centers offer an interdisciplinary approach to performing arts medicine.

Artists and performers provide many of the most memorable moments in our lives, and art is probably the most potent healing force known to humanity. The medical profession is increasingly recognizing its duty to help performing artists in their fight against pain and disease and to treat them and their ailments in the most humane and effective ways possible.

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Epitomes

Important Advances in Clinical Medicine

Psychiatry

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in psychiatry that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Advances in the Treatment of Alcoholism

A PUBLISHED DEFINITION OF alcoholism has been useful in both clinical practice and medical education. Alcoholism is described as a chronic primary disease. This research-based concept is useful in supporting abstinence-based treatment that links patients with alcoholism into the 12-step program of Alcoholics Anonymous. This new definition also supports the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised, describing loss of control over the use of alcohol and a continued use despite adverse consequences.

Abstinence from alcohol and other addicting drugs is now well accepted as a first goal in the treatment of alcoholism. Anxiety and depression, so commonly associated with alcoholism, usually clear with abstinence and continued treatment. A consensus has developed that, unless the emotional problems are severe enough to interfere with patients' ability to participate in treatment, chemotherapy—antidepressants—should not be started until two to eight weeks after detoxification has been completed.

The problems of a dual diagnosis of psychiatric disorders and alcoholism have become increasingly well recognized in treatment settings. These complex problems require combined treatment. In most clinical settings, this is best done concurrently, with the alcoholism and psychiatric treatment teams cooperating with one another. Criteria are still being developed for matching patients with a dual diagnosis with the most effective treatment.

A structured treatment of alcoholism, which emphasizes education, group therapy, family involvement, and an intense introduction to Alcoholics Anonymous, has recently received research attention. A controlled study of alcoholic employees found that those who entered Minnesota model abstinence-based inpatient treatment were significantly more likely to be abstinent and active in Alcoholics Anonymous than those who were only sent to Alcoholics Anonymous or who could choose their treatment. Costs were similar for each group.

Research continues to confirm the importance of Alcoholics Anonymous in achieving stable sobriety. Both prospective and retrospective studies have shown that going to the meetings is a significant ($P < .001$) predictor of sobriety; having a sponsor and using a phone list both significantly ($P < .05$) reduced the risk of relapse; and 91% of people with alcoholism who become sponsors are in stable sobriety at ten-year follow-ups.

Physicians, and especially psychiatrists, are in an excellent position to help these patients overcome their resistance to Alcoholics Anonymous. A program of recovery in Alcoholics Anonymous complements medical and psychiatric treatment and promotes normal growth and development.

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Clozapine Update

CLOZAPINE is a unique antipsychotic medication that is especially effective in patients suffering from treatment-resistant schizophrenia. Although clozapine was developed more than 30 years ago, its use was restricted in the United States because of the occurrence of agranulocytosis in 1% to 2% of patients after its release in Europe.

Current literature suggests that clozapine is also effective in patients with schizoaffective disorder, and studies are being done to test its efficacy in a variety of psychiatric disorders. Delusions, hallucinations, disordered

thought, and aggressive behaviors may all be dramatically alleviated when compared with the response to standard antipsychotic treatments. In patients with symptoms such as withdrawal and apathy, the response to clozapine may be particularly dramatic. Patients with chronic schizophrenia who take clozapine appear to have substantially improved quality of life compared with patients on standard neuroleptic treatments. Anecdotal reports suggest that clozapine may have special efficacy for patients with severe schizophrenia early in their illness. Clozapine doses range from 25 to 900 mg per day.

Clozapine is largely free of the extrapyramidal side effects that are so common with ordinary antipsychotics. Tardive dyskinesia (late, persistent, orofacial dyskinesia) from clozapine use is rare, and clozapine treatment has substantially lessened the symptoms of tardive dyskinesia in many patients.

Clozapine's neurochemical profile is complex. A basis for its unique action may be a particular pattern of preference for D_2-dopamine receptors over D_1 receptors. Clozapine also has a complex relationship with serotonin, γ-aminobutyric acid, muscarinic, and other systems in the brain.

The manufacturer requires that a patient's weekly leukocyte count be above an "agranulocytosis threshold" of 2×10^9 per liter (2,000 per μl) before each week's supply of medication is released. Monitoring the granulocyte count to a threshold of 1 granulocyte $\times 10^9$ per liter (1,000 per μl) may be a more sensitive indicator. Half of reported episodes of agranulocytosis occur within three months of starting treatment, but weekly monitoring of leukocyte counts continues indefinitely. When agranulocytosis occurs, 14 days of isolation from exogenous infectious agents are usually necessary until the granulocyte count recovers. Treatment with filgrastim (granulocyte colony-stimulating factor) reduces the average duration of clozapine-induced agranulocytosis to about seven days.

Other side effects seen with clozapine use include fever, seizures, constipation, tachycardia, sedation, and sialorrhea. About 5% of patients will have a seizure at doses of more than 600 mg per day. These patients can usually be treated with a dosage reduction and divalproex sodium maintenance. Tachycardia and fever are both common when clozapine treatment is started. Rapidly raising the dose above 300 mg, using the necessary titration schedule, seems to be the best way to manage fever. Severe constipation can occur and can require aggressive bowel management. A dose-dependent sialorrhea is a puzzling side effect in a medication that otherwise has strong anticholinergic properties.

Despite its side effects and the required intensive monitoring, clozapine remains a uniquely effective medication in the management of treatment-resistant schizophrenia.

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Dementia Complex of the Acquired Immunodeficiency Syndrome

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) dementia complex, also known as human immunodeficiency virus (HIV-1)-associated dementia complex, is the most common central nervous system complication of HIV infection. It is characterized by deficiencies in cognition-motor performance and sometimes behavioral changes. Although the natural history and severity of this complex can vary and the actual incidence is debated, AIDS dementia complex causes serious morbidity and mortality in a considerable number of people with AIDS.

The AIDS dementia complex is a severe form of HIV-1-associated cognitive-motor complex that includes a broad spectrum of clinical manifestations and severity. Early symptoms can be subtle and apparent only with neuropsychological testing. Severe symptoms include global cognitive and motor dysfunction with florid dementia and death. Key cognitive symptoms of this complex include memory loss, decreased concentration, decreased attention span, and visuospatial disorientation. Patients often have behavioral changes such as apathy, loss of interest in usual activities, social isolation (withdrawal), or irritability. Because AIDS dementia complex is a subcortical dementia, early motor deficits are common. In particular, generalized slowing, ataxia, tremors, incoordination, lower extremity weakness, spasticity, and hyperreflexia can develop. This is different from Alzheimer's disease and other cortical dementias that present with more obvious intellectual deterioration. The deficits of AIDS dementia complex are like a record that is being played too slowly; those of Alzheimer's disease, in contrast, are more like a record that skips.

Clearly the symptoms of AIDS dementia complex overlap with those of other affective psychiatric and neurological disorders. For example, depression, drug intoxication, delirium, neurosyphilis, cryptococcal meningitis, toxoplasmosis, lymphoma, and progressive multifocal leukoencephalopathy are all important in the differential diagnosis of patients with mental status changes. A thorough workup is imperative to rule out these disorders that require different treatment methods. Evaluation should include a cranial imaging study (preferably a magnetic resonance imaging scan, which is more sensitive than computed tomography) with contrast enhancement and a lumbar puncture for cerebrospinal fluid studies. Neuropsychological testing can provide a quantitative serial assessment with early AIDS dementia complex, but it is usually not a major tool in diagnosis.

Although this complex is not considered curable, interventions can stabilize or reverse symptoms and improve living function, even with advanced symptoms. For cognitive impairment, high-dose zidovudine (1 to 2 grams orally per day) continues to be the most effective treatment. Other antiretrovirals, with the possible exception of stavudine (d4T), do not readily cross the blood-brain barrier. Human immunodeficiency virus type 1 is thought to cause neuronal death not by direct viral infection, but indirectly by generating toxic products such as HIV gp120 and cellular cytokines (interleukins, tumor necrosis fac-

tor). Two promising treatments are nimodipine (Nimotop), which blocks gp120-mediated calcium channel damage, and pentoxifylline (Trental), which may suppress the production of tumor necrosis factor. Psychotropic medications can be effective in selected cases; for example, low-dose antipsychotic agents can be given for impulse control or psychostimulants for lethargy and withdrawal. Mania, anxiety, and depression are also common and should be aggressively treated.

Unfortunately, many patients with moderate to severe AIDS dementia complex cannot be safely managed in the community or receive appropriate intervention in an acute-care hospital setting. A model inpatient program was established in San Francisco in February 1991 to treat persons with moderate to severe HIV-1-associated AIDS dementia complex using a multidisciplinary medical-psychiatric cost-effective rehabilitation model of care. All the patients have advanced HIV disease (average $CD4^+$ count, 46×10^6 per liter) and need both psychiatric and medical intervention. More than half of these patients have been discharged to home or to a lower level of care in the community. In summary, AIDS dementia complex is a complication of advanced HIV disease that needs to be aggressively diagnosed and treated. With appropriate interventions, profound differences can be made in the lives of people with this complex.

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Brain-Gut Interactions

FUNCTIONAL GASTROINTESTINAL (GI) disorders, such as the irritable bowel syndrome, have long been associated with psychological distress. The exact relationship between psychiatric disorders and these functional disorders has not been accurately described, however. The diagnostic criteria for functional GI disorders have never been precisely defined, and criteria for inclusion or exclusion of a specific functional diagnostic disorder have not existed. Rather, patients have been diagnosed with "functional abdominal pain," "chronic gastritis," or "irritable bowel syndrome" after obvious organic disease has been excluded.

Major advances in the past three years, both in nomenclature and the development of validated screening questionnaires, have enabled more accurate descriptions of the incidence and prevalence of functional GI disorders. An international working group has established specific diagnostic criteria, modeled on the revised third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) of the American Psychiatric Association. Consequently, validated behavioral criteria for the more than 20 subgroups of functional GI disorders have been defined.

The development of accurate and discriminating diagnostic criteria has coincided with research findings that describe the specific psychic traumas that are particularly likely to produce symptoms of functional GI disorders.

The discovery that specific psychiatric disorders, particularly anxiety disorders, occur concomitantly with the irritable bowel syndrome is a second avenue of progress. There is also evidence that patients with the irritable bowel syndrome have an excessive incidence of major depression compared with controls. A recent study has shown that panic disorder, generalized anxiety disorder, and major depressive disorder are likely to occur in patients with the irritable bowel syndrome. In this study, 26% of patients met the DSM-III-R criteria for panic disorder alone.

These studies also found that when patients were treated for their psychiatric disorders, their gastrointestinal symptoms resolved independent of any specific GI intervention. The implications of these findings are obvious. Indeed, in one study substantial improvement in the patients' irritable bowel syndrome was shown when they were treated for generalized anxiety disorder with alprazolam.

The ability to describe accurately specific functional GI disorders and to recognize that these disorders are related to certain psychosocial stressors such as physical and sexual abuse is critical to resolving both the psychiatric and GI problems. Likewise, the high incidence of specific psychiatric disorders in patients with certain functional GI disorders challenges clinicians to examine these comorbid associations and to simultaneously treat patients' GI and psychiatric symptoms. It is important to note that patients who present with functional GI symptoms often display considerable alexithymia, or an inability to express emotions. The clinician should be especially careful to take a psychiatric history that specifically addresses major depression, panic disorder, generalized anxiety disorder, and other anxiety disorders, such as obsessive-compulsive disorder. The future holds promise for the development of even more specific diagnostic and therapeutic modalities to help us understand these complex and distressing conditions.

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Major Complications of Neuroleptic Drug Use

NEUROLEPTIC OR ANTIPSYCHOTIC drugs are the primary short-term and maintenance therapy for schizophrenia and other psychotic disorders. In addition to causing acute dystonic reactions, akathisia, and parkinsonism—all of which are usually reversible with the discontinuation of the neuroleptic drug—these agents can cause irreversible tardive movement disorders. The usual estimate of risk for tardive dyskinesia is 20% to 30% after many years of

neuroleptic exposure, although a recent survey projected a risk of 68% after 25 years of exposure. Tardive dystonia carries a risk of only 1% to 2% but causes movements that are profoundly disabling and disfiguring. Some patients with tardive dystonia may benefit from therapy with the atypical neuroleptic clozapine, and many dystonic signs can be alleviated by periodic injections of botulinum toxin.

Although the incidence of the neuroleptic malignant syndrome has been a subject of debate, recent prospective studies suggest it is less than 0.1%. This life-threatening condition is characterized by hyperthermia and other autonomic instabilities, an altered mental state (from confusion through coma), rigidity and other extrapyramidal signs, and laboratory abnormalities, often including elevated creatine kinase levels and leukocyte counts. The neuroleptic malignant syndrome tends to occur early in the treatment course and with higher and more rapidly rising doses. The need for supporting vital signs in this condition is apparent, but the effectiveness of purported antidotes—namely dantrolene sodium, bromocriptine mesylate, and amantadine hydrochloride—has been contested.

Probably all neuroleptics lower the seizure threshold. This is not usually a problem, except when patients overdose, have underlying seizure disorders, withdraw from sedative-hypnotic agents, or take other proconvulsant medications. The use of clozapine, however, is associated with a relatively high incidence of seizures, particularly at higher doses. The incidence of seizures is 1% to 2% for doses of 300 mg per day, 3% to 4% for 300 to 600 mg per day, and 5% for 600 to 900 mg per day.

Although other antipsychotic drugs have rarely caused agranulocytosis, clozapine has been associated with about a 1% risk. Ashkenazi Jews may be at an elevated risk, and recent evidence suggests that HLA tissue typing may correlate with risk. If clozapine is stopped immediately and patients protected from intercurrent infection, full recovery can occur. The mechanism of agranulocytosis appears to be allergic rather than toxic, and patients must never be reexposed.

The administration of lower potency neuroleptics—most notably thioridazine hydrochloride and clozapine—is associated with electrocardiographic changes and can have clinical consequences. This is more likely to be a problem in overdoses, in patients with preexisting heart disease, or when neuroleptics are administered with drugs with comparable cardiac actions—such as quinidine-like effects, calcium channel blocking properties, or antiadrenergic activity.

Neuroleptics have been available for use for about four decades. They have been a godsend for many patients with chronic mental illnesses, and they have also alleviated nausea and gastroparesis in many others. Physicians prescribing these agents, however, need to be aware of their many, varied, and occasionally hazardous side effects. Clozapine has ushered in a new era of neuroleptic pharmacotherapy with powerful therapeutic benefits counterbalanced by serious toxicity. Over the next few years, we should see a new series of benzamides and other atypical neuroleptics that should broaden the ranges of both benefits and side effects.

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Mitigating Posttraumatic Stress Disorder

FIRST ACKNOWLEDGED as a distinct diagnostic disorder with the 1980 publication of the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, posttraumatic stress disorders are recognized today as valid and treatable psychiatric problems. Triggered by a traumatic event that is outside the range of usual and common human experience, symptoms manifest themselves as three clusters: the mental reexperiencing of the traumatic trigger event, the avoidance of sensory stimuli that have become associated with the trauma, and persistent hyperarousal of the autonomic nervous system.

Earlier research focused on identifying the characteristics of the trauma that stimulate posttraumatic stress disorder reactions and identifying specific risk factors. Survivors of natural disasters are more likely to have symptoms of reexperiencing the trauma, whereas those who have witnessed violence perpetrated by people are more likely to demonstrate avoidance and denial. Recently the contribution of genetic factors in individual vulnerability to posttraumatic stress disorder was shown in a study of 4,042 pairs of Vietnam-era monozygotic and dizygotic male twins. Posttraumatic stress disorder-spectrum symptoms in monozygotic pairs with exposure to combat were more highly concordant.

Symptom intensity in this complex group of disorders is the result of the interaction of many genetic and environmental factors. Their relative contributions await further study, but it holds that improving what is improvable, namely, a person's environment, can have a profound ameliorating effect on the development and the course of these disorders.

There is immense practical value to a health care system facing the prospect of massive casualties to train triage physicians to recognize psychological traumas. The patients suffering acute traumatic stress disorders can be diverted to a nonhospital treatment site that does not reinforce the sickness role. This also frees up hospitals and their medical personnel to concentrate on treating patients needing urgent surgical therapy. During the Persian Gulf War, about 43% of patients admitted to a hospital following Scud missile attacks on Israeli cities had purely psychological trauma. Secondary triage to separate patients with psychological trauma from those with physical injuries lessens the burden on a stressed emergency care system.

Trauma survivors are faced with shattering realities: the loss of a sense of safety and stability, an awareness

that they can easily be rendered totally helpless by circumstance, and a forced confrontation with their own mortality. "Secondary wounding" with extension of the trauma can occur when medical and other caregivers manifest attitudes that suggest disbelief or blaming the patients for causing their own trauma. Implications that trauma survivors should have been more cautious, more intelligent, more resistant, or more morally outraged tend to be directed particularly to the victims of human-caused disasters. This unnecessary worsening of the original trauma, when based on a health worker's ignorance, burnout, or personal belief system, can be avoided. Secondary wounding can also occur at the hands of fellow trauma survivors, who happen, at that point in time, to be coping with their own losses by the use of denial of the adverse consequences.

A natural result of primary and secondary trauma is internalization of the victim status. Though no longer in a traumatic situation, such patients adopt the disaster and its aftermath as the central, dominating event in their lives. They then use it to determine their general worldview and the way they think and act. Secondary prevention efforts must address these attitudes that underlie the "permanent victim" status: intolerance of one's mistakes and fear of seeming defective, weak, or cowardly. Research has shown that primary prevention in the form of rapid, brief psychiatric intervention and the use of support groups can minimize the development of persistent posttraumatic stress disorder symptoms. The short-term use of benzodiazepine or antihistamine agents with anxiolytic or hypnotic effects can be helpful in selected patients not prone to chemical dependency.

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Sexual Victimization and Physical Symptoms in Women

THERE IS A GROWING AWARENESS that childhood sexual abuse causes not only psychological sequelae but also continuing medical morbidity. Sexual victimization can be associated with several long-term physical effects.

Several recent, well-designed studies have associated sexual victimization with a variety of medical conditions, particularly chronic pelvic pain and the irritable bowel syndrome. Surveys of participants of health maintenance organizations have also shown increased rates of smoking, obesity, excessive alcohol and drug use, pregnancy before age 18, abortions, multiple sex partners, high-risk sexual contacts, a greater number of unintended pregnancies, earlier first intercourse, and a decreased frequency of Pap smears for survivors. They have also been shown to be higher users of medical care resources, averaging two to three times the usual rates of clinic attendance.

The health care use of survivors may also be influenced by social and psychological factors. A higher use may arise from the inability of a woman's family of origin to protect her from the abusive relationship or to provide early medical intervention and ensuing psychological care. Subsequent contacts with health care professionals may afford opportunities for the survivors to obtain this emotional support from their medical caregivers, thus reinforcing somatization and increased health care use.

The Council on Scientific Affairs of the American Medical Association has recently issued a special report declaring the need for an increased awareness on the part of physicians of all forms of violence against women. The report suggested guidelines for physician training in assessing past victimization as part of the routine care of women. Given the prevalence of sexual victimization, it is likely that physicians come into daily contact with a substantial number of sexual victimization survivors. Greater awareness of the long-term biopsychosocial effects of sexual victimization may be a critical aspect of improving care for these patients.

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Role of Newer Antidepressants

NEWER ANTIDEPRESSANTS are gradually replacing old tricyclic antidepressants because of comparable efficacy with fewer side effects and a much lower risk of death from overdose. Newer-generation antidepressants include trazodone hydrochloride, bupropion hydrochloride, and the selective serotonin reuptake inhibitors fluoxetine hydrochloride, sertraline hydrochloride, and paroxetine.

Trazodone and bupropion, unlike tricyclic antidepressants, are ineffective for panic. Anticholinergic effects—dry mouth, blurred vision, constipation, and urinary retention—and cardiovascular effects are less with the newer drugs than with tricyclic antidepressants. Weight loss can occur with bupropion and fluoxetine. Overdose lethality is rare with these newer drugs.

Newer antidepressants, like tricyclic antidepressants, show efficacy at two to six weeks, and about 50% to 70% of depressed patients obtain benefit. Patients who partially respond or do not respond may benefit from lithium or triiodothyronine augmentation or by changing to a different class of drug, such as from trazodone to serotonin reuptake inhibitors and serotonin reuptake inhibitors to bupropion.

Trazodone is highly sedating, and dose titration to the maximum tolerated dose is required in the 100-mg to 600-mg at bedtime range based on daytime sedation. Trazodone, 50 mg to 100 mg, is widely used as a hypnotic in lieu of potentially addicting medications. It may wors-

en preexisting ventricular arrhythmias. It causes priapism in about 1 in 7,000 men.

Bupropion is highly activating, may benefit adults with attention deficit disorder, and has the advantage among antidepressants of causing no sexual dysfunction. It has the disadvantage, however, of a higher seizure risk than tricyclic antidepressants. Patients with eating disorders, head trauma, seizure history, or who are taking other drugs that lower the seizure threshold (such as theophylline) should not receive this drug. The dosage is 300 to 450 mg daily and must be divided.

Fluoxetine, the first marketed serotonin reuptake inhibitor, has now been shown to be beneficial in many conditions including depression, mixed anxiety-depression, anorexia, bulimia, panic, and obsessive-compulsive disorder. The other serotonin reuptake inhibitors, sertraline and paroxetine, will probably show a similar spectrum of action and have the advantage of a shorter half-life to allow for more rapid dose adjustment and washout in case of intolerance. Selective serotonin reuptake inhibitor antidepressants may be lethal in combination with monoamine oxidase-inhibitor antidepressants.

Both bupropion and paroxetine carry less risk of precipitating mania in patients with bipolar depression than do tricyclic antidepressants.

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Alerts, Notices, and Case Reports

Probable Quinine-Induced Hepatotoxicity

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QUININE PREPARATIONS affect many biologic systems and are most widely used in the treatment of nocturnal leg cramps.[1] In fact, a recent double-blind crossover trial demonstrated the effectiveness of quinine for this problem.[2] Adverse effects of quinine range from cinchonism manifested as nausea, vomiting, tinnitus, and deafness to various hypersensitivity reactions. These reactions may present as generalized rash or pruritus or may be organ specific. An unusual effect of hypersensitivity to quinine is hepatotoxicity. Hepatic injury has been more commonly reported with the use of quinidine, its optical isomer, which generally leads to the development of granulomatous hepatitis.[3]

Three cases of quinine hepatotoxicity have been reported, occurring as an acute illness characterized by fever, nausea, and malaise associated with moderately high levels of aminotransferase.[4-6] Liver biopsy was done in two of the cases and revealed granulomatous hepatitis.[5,6] Withdrawal of the drug resulted in a dramatic resolution of both clinical findings and liver function abnormalities. The reversibility of this condition attests to the importance of its detection in patients taking quinine-containing preparations in whom high levels of aminotransferase are recorded. We report the fourth case of probable quinine-induced hepatotoxicity presenting with mixed hepatocellular and cholestatic features.

Report of a Case

The patient, a 74-year-old man, was seen because for two days he had had back and right upper quadrant pain, fever, and jaundice. Right hemiplegia was present from a stroke suffered in August 1990. The patient was receiving fosinopril sodium for hypertension. A month before admission he noted nocturnal cramping in the left calf. Treatment with quinine sulfate, 260 mg at bedtime, was initiated. No other medications were recently prescribed. There was a remote history of alcohol use and no history of hepatitis. Liver function tests done a year previously showed normal values.

On admission the patient appeared ill, and scleral icterus was noted. His blood pressure was 159/78 mm of mercury, pulse rate 83 beats per minute, and temperature 38.7°C. He had mild right upper quadrant tenderness. Laboratory studies revealed a leukocyte count of 10.6×10^9 per liter with 0.90 segmented cells, 0.07 lymphocytes, and 0.03 monocytes. The total bilirubin concentration was 123 μmol per liter (7.2 mg per dl) and 94 μmol per liter (5.5 mg per dl) conjugated. The alkaline phosphatase level was 314 units per liter (normal, 37 to 107), alanine aminotransferase 241 units per liter (normal, 3 to 36), and aspartate aminotransferase 209 units per liter (normal, 27 to 47). A urinalysis revealed no abnormalities. The Westergren sedimentation rate was 65 mm per hour. Serologic studies were negative for hepatitis A, B, and C. Ultrasonography on admission showed thickening of the gallbladder but no biliary dilatation or stones. A computed tomographic scan of the abdomen revealed a slightly enlarged but homogenous liver. No pancreatic masses or biliary disease was found. Both fosinopril and quinine were withdrawn.

Because of the atypical presentation and the absence of biliary dilatation or stones, on day 2 of the patient's hospital stay, a percutaneous liver biopsy was done that revealed inflammatory infiltrates composed of lymphocytes, plasma cells, and neutrophils in the portal area. Microgranulomata were observed that contained circumscribed areas of necrotic hepatocytes surrounded by neutrophilic infiltrates. Substantial cholestasis was noted. Over five days of his stay in the hospital, the patient's total bilirubin concentration declined to 39 μmol per liter (2.1 mg per dl) and the alanine aminotransferase from 241 to 85 units per liter. Laboratory tests done to exclude other causes of granulomatous hepatitis, including antinuclear antibody, purified protein derivative skin test, *Coccidioides immitis* serologic test, and complement levels were nondiagnostic. The patient was seen in follow-up two weeks later with normal indices of liver function.

Discussion

This is the fourth reported case of probable quinine hepatotoxicity. Although the medication was not readministered, the withdrawal of quinine therapy was associated with the rapid return of liver function test values to nearly normal. The toxic reaction completely resolved within two weeks. Fosinopril had also been withdrawn on admission, but the patient at discharge was taking lisinopril and since August 1992 has tolerated the drug without adverse effects. A review of the literature regarding angiotensin-converting enzyme inhibitors elicited no reports of cholestatic hepatitis related to the use of fosinopril. Several cases of hepatotoxic reactions from enalapril, captopril, and lisinopril have been reported, and granulomata in the liver have been infrequently found.[7-10] In the case reported here, a liver biopsy specimen revealing the presence of microgranulomata is more consistent with the findings of previously reported cases of quinine hepatotoxicity.[5,6]

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The dramatic presentation of this disorder with fever and mixed hepatocellular and cholestatic liver function abnormalities suggests alternative diagnoses, but inquiry regarding quinine use is helpful. This commonly used remedy for a frequent clinical problem, especially among elderly patients, justifies increased awareness of this little-recognized manifestation of quinine use.

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Severe Atypical Behçet's Syndrome

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BEHÇET'S SYNDROME is a chronic relapsing inflammatory condition of unknown cause.[1,2] Major clinical features of this syndrome include recurrent aphthous stomatitis, genital ulcers, cutaneous vasculitis, uveitis, synovitis, and meningoencephalitis,[1-6] although any organ may be affected by the multisystemic vasculitis that characterizes this disorder.[5,6] No pathognomonic clinical, serologic, or pathologic features have been identified. The diagnosis continues to be based on the recognition of a number of compatible clinical manifestations of the syndrome. An international study group recently agreed that diagnosis should be based on the presence of recurrent oral ulcers associated with at least two of the following criteria: genital ulcers, uveitis, typical skin lesions, or confirmed pathergy (the formation of a sterile cutaneous pustule at the site of a needle puncture).[6] Diagnosis is often complicated by the asynchronous and delayed appearance of key clinical features of Behçet's syndrome in a given patient.[1,3] Corticosteroid treatment continues to be important,[1-3,5] but recent evidence indicates that cytotoxic therapy with an agent like chlorambucil may be necessary to arrest severe manifestations of Behçet's vasculitis such as uveitis and meningoencephalitis.[5,7]

We report a case with features of Behçet's syndrome causing severe multisystemic disease in a young man. This case is unique because of the rapid clinical evolution of life-threatening disease, the severity of end-organ effects, and the successful use of intravenous pulse-dose cyclophosphamide therapy.

Report of a Case

A previously healthy 34-year-old man presented to the Harborview Medical Center, Seattle, Washington, with polyarthritis and a rash. Two weeks before admission, he had a cough productive of scant white sputum, and redness and pain developed in his left eye. Three days before admission, he had fever, rigors, left hip pain, and swelling of the elbows. On the day before admission, a mildly pruritic rash developed on his face that spread to involve his chest, back, and arms. With the onset of postural lightheadedness and diffuse myalgias, he came to the hospital and was admitted. The past medical history was notable for several episodes of penile shaft ulceration that resolved without medical attention. There was no history of headache, photophobia, visual changes, nausea, vomiting, diarrhea, dysuria, urethral discharge, or insect bites.

On examination the patient was thin and grimaced in pain with movement of his extremities. His temperature was 37.5°C, the pulse rate was 120 beats per minute, respirations were 18 per minute, and the blood pressure was 130/100 mm of mercury. A cutaneous eruption consisting of scattered pustules and papules with hemorrhagic crusts and surrounding erythema involved the face, upper trunk, and arms (Figure 1). The palms, nail beds, and lower body were spared. The left conjunctival membrane was injected; the fundi and uveal structures were normal. There were several small buccal mucosal ulcers. No heart murmur was heard. The liver and spleen were not enlarged. A small ulcer of the dorsal penile shaft was present. The elbows, knees, and right ankle were inflamed and swollen in a fusiform pattern. Passive range of motion produced severe discomfort though no effusions were evident. Initial laboratory data included a normal hematocrit, platelet count, serum chemistry values, and urinalysis. The leukocyte count was 13.0×10^9 per liter (normal 4.3 to 10.0). The blood smear and leukocyte differential count were normal, as were prothrombin and activated partial thromboplastin times. Two blood specimens and a urethral specimen were obtained for culture.

A presumptive diagnosis of disseminated gonococcal infection was made, and empiric antibiotic treatment was initiated. On the second day of the hospital stay, fever and fusiform swelling of the hands, wrists, and forearms de-

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Figure 1.—The patient's face on the third day of hospitalization shows crusting hemorrhagic papules and pustules.

veloped. Specimens were obtained from an unroofed pustule for herpes group immunofluorescent staining and culture. Two days later, he remained febrile with more pronounced periarticular inflammation and the continuing development of new skin papules in the involved areas. All cultures remained negative for bacterial or viral organisms. A punch biopsy specimen of an upper chest papule revealed focal perifollicular dermal and epidermal infiltrates of neutrophils without cytopathic or vasculitic changes (Figure 2). Based on a provisional diagnosis of Sweet's syndrome, all antimicrobial agents were stopped and a regimen of prednisone, 80 mg orally per day, was begun. Within 48 hours, substantial resolution was noted in the rash and periarticular inflammation.

On the fifth day of his hospital stay, however, the patient had nausea, vomiting, and painful abdominal distention due to intestinal ileus demonstrated by abdominal radiographs. Over the ensuing 48 hours, the abdominal symptoms worsened and occult blood was noted in the stool. Tachypnea developed, and a lobar infiltrate was noted on a chest radiograph. Broad-spectrum antibiotic therapy was resumed after additional specimens for culture were obtained. New crusted pustules were noted at several antecubital venipuncture sites. Biopsy of an antecubital pustule revealed histologic features identical to those of the original skin biopsy. Serial abdominal radiographs revealed increasing bowel dilatation with irregular bowel wall thickening, and culture of blood drawn on the seventh day of his hospital stay grew *Serratia marcescens*. On the tenth day of his hospital stay, the patient had diffuse pulmonary infiltrates and acute respiratory failure requiring the use of an endotracheal tube and mechanical ventilation. Endotracheal secretions were bloody. Vasopressor infusions were necessary to maintain adequate blood pressure. A pericardial friction rub was noted, and an electrocardiogram revealed diffuse ST-segment elevation consistent with acute pericarditis. Echocardiography showed normal valves and a large pericardial effusion without evidence of pericardial tamponade. Obtundation prompted a computed tomographic scan of the head and cerebrospinal fluid examination, both yielding normal results. Despite the substitution of intravenous methylprednisolone sodium succinate, 1 gram three times a day, for prednisone and the addition of intravenous immune globulin, 1 gram per day, no notable clinical improvement was evident by the 12th day of hospital stay.

Based on the suspicion of an underlying aggressive systemic vasculitis, cyclophosphamide, 1 gram, was administered as a single intravenous dose. Substantial clinical improvement over the next five days led to successful

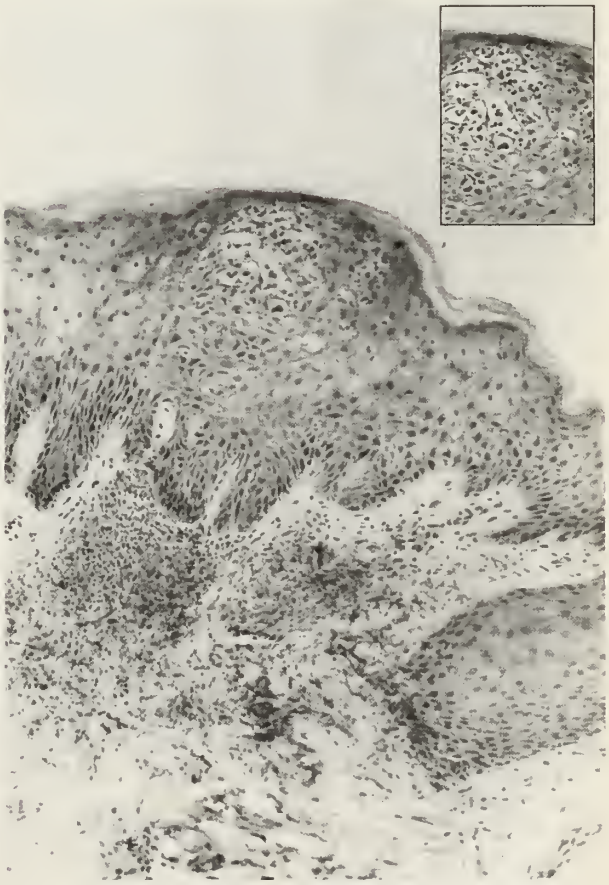

Figure 2.—A punch biopsy of the skin (original magnification × 200) shows dermal and epidermal edema and dense focal acute inflammatory infiltration. No distinct vasculitic changes are present. The inset shows a focal epidermal collection of neutrophils.

removal of the endotracheal tube. His ileus resolved, permitting oral intake, and the patient was moved from the intensive care unit on the 24th day in the hospital. Nine days later, all signs of rash, mucosal ulceration, and arthritis had resolved. Chest radiographs and electrocardiograms had returned to normal. The patient was discharged in satisfactory condition on a maintenance regimen of prednisone, 30 mg orally twice a day, and chlorambucil, 4 mg orally per day. Additional laboratory studies included tests for human immunodeficiency virus antibody, syphilis, antinuclear antibodies, and rheumatoid factor, all of which were negative. Human leukocyte antigen typing revealed the presence of HLA-B45 and B49 antigens but not HLA-B5, B27, or B51.

Over the 12 months since discharge, prednisone and chlorambucil have been tapered to doses of 5 mg daily and 1 mg daily, respectively. Penile ulcers have recurred on several occasions; a painful knee effusion occurred once. No increases in drug doses have been necessary. There has been no recurrence of rash or gastrointestinal or cardiopulmonary symptoms. Adverse effects have been limited to mild asymptomatic aminotransferase elevations and facial acne that responded to oral antibiotic therapy.

Discussion

Our patient had aphthous stomatitis associated with recurring genital ulcers, cutaneous pustules, synovitis, and cutaneous pathergy—all major features of Behçet's syndrome.[1,5,6] Less common features including pulmonary hemorrhage, pericarditis, and enteritis also developed. Neither uveitis nor meningoencephalitis was observed. A diagnosis of Behçet's syndrome best explains our patient's clinical presentation. Although recurrent aphthous stomatitis is a necessary part of the case finding definition of Behçet's syndrome, it is recognized that a small percentage of patients have no oral mucosal involvement.[6] Crohn's disease may present in a remarkably similar manner.[8] The diagnostic distinction often requires intestinal biopsy,[9,10] which our patient did not undergo. The arthritis of Crohn's disease typically occurs after chronic intestinal symptoms.[8] This feature and the presence of cutaneous pathergy favor a diagnosis of Behçet's syndrome. Gram-negative bacteremia undoubtedly complicated our patient's course but occurred after seven days in the hospital and was likely due to gut mucosal involvement by his primary inflammatory disease.

Behçet's syndrome has been observed primarily in Asian and Eurasian populations,[4] but rarely reported in African Americans. Although the clinical course of Behçet's syndrome is variable, in our patient it was unusually accelerated and severe. Interestingly, it is thought to be more severe in young men and most remittent in older women.[2,11]

A wide variety of skin lesions, all considered to be manifestations of cutaneous vasculitis, have been observed in Behçet's syndrome. These include papules, pustules, vesicles, pyoderma, folliculitis, and nodules resembling erythema nodosum.[1,3,4] Our patient presented with a pustular eruption of the face and upper trunk that rapidly developed hemorrhagic characteristics. Biopsy of one of these lesions revealed structural features closely resembling those described in Sweet's syndrome.[12] An acute neutrophilic dermatosis with clinical features of Sweet's syndrome is a rare but recognized presentation of Behçet's syndrome. As in our patient, these skin lesions usually respond rapidly to treatment with parenteral corticosteroids. In addition, our patient showed considerable cutaneous pathergy.[13] This curious phenomenon is common in Turkish patients with Behçet's syndrome; being unique to Behçet's syndrome, it is rare in white patients.[14] Biopsy of a pathergic lesion from our patient revealed structure remarkably similar to that observed in the spontaneous lesion.

A symmetric arthritis affected the ankles, knees, wrists, and elbows of our patient. Recurrent seronegative arthritis, primarily involving the knees, ankles, and wrists, is noted in 50% to 60% of patients.[1-3,15] It is usually nondestructive and steroid responsive, as in our patient.

Involvement of the cardiovascular system is reported in 7% to 29% of patients.[3] The predominant manifestations are arterial aneurysms, superficial thrombophlebitis, and thromboses of large veins and arteries.[1-3] End-organ infarction, including myocardial infarction in young patients, can occur. A large pericardial effusion developed in our patient, and he had pronounced electrocardiographic changes of pericarditis, a complication rarely reported in the literature.[3]

Gastrointestinal involvement, as seen in our patient, is a rare manifestation. The clinical presentation usually mimics Crohn's disease of the colon with discrete ulcers involving any portion of the large bowel and occasionally the distal ileum.[1,3,9,10] Perforations of the large bowel and ileum requiring emergent surgical intervention have been reported.[1,10] Our patient's gastrointestinal complications were limited to hemorrhage and ileus that responded to medical therapy. Endoscopic evaluation was deferred.

Pulmonary involvement in Behçet's syndrome occurs in about 5% of cases and tends to be associated with disease exacerbation at other sites.[16,17] Patients usually present with hemoptysis associated with fever, chest pain, and dyspnea. The most common radiographic abnormalities are segmental infiltrates or rounded opacities that have been shown to correlate with regions of pulmonary hemorrhage.[16,17] When done, pulmonary angiography may show arterial thromboses, emboli, and aneurysms. Pulmonary vasculitis, possibly due to circulating immune complexes, is thought to underlie these manifestations. Clinical evidence suggests that anticoagulant therapy is contraindicated. Pulmonary hemorrhage was a prominent feature of our patient's illness. He did not undergo definitive angiographic evaluation.

Systemic corticosteroids continue to be useful therapy for most manifestations of Behçet's syndrome.[1,3,5] As happened in our patient, corticosteroid therapy often leads to rapid control of skin, mucosal, and joint inflammation. The management of severe Behçet's syndrome remains more problematic. Supplemental therapy with other immunomodulatory agents is often necessary to control

serious manifestations such as uveitis and meningoencephalitis and to reduce the incidence of long-term steroid toxicity.[5,7] Various oral agents including azathioprine, colchicine, cyclophosphamide, chlorambucil, levamisole hydrochloride, cyclosporine, thalidomide, and dapsone have been used for this purpose.[7,18-24] One report suggests that plasma exchange may be beneficial in maintaining disease remission.[25]

Because of the benefit of high-dose cytotoxic therapy in other diseases associated with fulminant necrotizing systemic vasculitis, such as Wegener's granulomatosis and polyarteritis nodosa,[26] we chose to administer pulse-dose intravenous cyclophosphamide to our patient in an attempt to arrest the course of his illness. Although the possibility of a coincidental spontaneous remission cannot be excluded, this treatment, in conjunction with immune globulin and high-dose corticosteroid therapy, was followed by a dramatic clinical remission. After gastrointestinal motility had recovered, maintenance therapy with oral chlorambucil and prednisone was initiated. There has been no evidence of serious disease relapse during the 12 months of subsequent care, although recurrent arthritis and genital ulcers have justified ongoing therapy.

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Special Series

Paying for Long-term Care

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Everyone agrees that insurance for long-term care is inadequate in the United States. Disagreement exists, however, on whether such insurance should be provided through the private or public sector. Private insurance generally uses the experience-rating principle that persons with higher risk of illness are charged higher premiums. For private insurance for long-term care, this principle creates a dilemma. Most policies will be purchased by the elderly; yet, because the elderly have a high risk of needing long-term care, only about 20% of them can afford the cost of premiums. A public-private partnership by which the government partially subsidizes private long-term-care insurance is unlikely to resolve this dilemma. Only a social insurance program for long-term care can provide universal, affordable, and equitable coverage.

(Estes CL, Bodenheimer T: Paying for long-term care. West J Med 1994; 160:64-69)

This article is another in our series on health care reform.

Long-term care is an issue of growing importance to practitioners and policy makers. Projections of the growth in the elderly population are startling. In 1990, Americans older than 65 years numbered 31 million; this figure is expected to reach 52 million by the year 2020 and 68 million by 2040. By 2050 more than 20% of the population will be 65 or older. Three million Americans were older than 85 years in 1990; those 85 and older are the fastest-growing age group in the United States; their number will more than double to 7 million by the year 2020 and will quintuple, rising as high as 24 million by 2050.[1-4] In addition, millions of disabled Americans younger than 65 need long-term care.[5]

Practicing physicians repeatedly come face to face with the problem of long-term-care financing. An elderly man with a disabled wife suffers a devastating stroke, requiring nursing home placement; within nine months the family's life savings are spent. A woman living alone develops Alzheimer's dementia; the woman's daughter is forced to abandon her career and care for her mother because funds are not available to hire the needed 24-hour-a-day help. A near-fatal auto accident converts an 18-year-old boy into a quadriplegic, turns his mother into a full-time unpaid caregiver, and throws the family into poverty. Time and again, physicians witness the tragedy of chronic illness compounded by the failure of our health insurance system to cover the long-term needs that the illness creates.

Although agreement is universal that financing long-term care is a serious problem, opinions diverge widely on the best solution.* We describe the realities of long-term care, examine the difficulties faced in applying private insurance principles to long-term care, and evaluate three options for financing—private insurance, public-private partnership, and social insurance. We conclude that social insurance is the most reasonable approach to financing long-term care for all Americans.

The Reality of Long-term Care

At present, 9½ million Americans need long-term care; of these, 3.9 million are disabled persons younger than 65 and 5.6 million are 65 years or older.[5] Americans older than 85 years are the group most likely to need long-term care because about half are disabled or need help with one or more activities of daily living.[6] Men older than 65 have a 30% chance of entering a nursing home at some time in their lives, whereas for women—who more often outlive their spouses—the chance is 52%.[7]

Medicare was designed primarily to cover the costs of hospital care and offers limited coverage for long-term care; only 6% of long-term-care costs are covered by Medicare.[8] Only about 4% of elderly persons have private long-term-care insurance; only 1% of nursing home costs are covered by private policies.[9] About 7% of the population incurs catastrophic expenses for nursing home care, such as payments that exceed 20% of their income. When both acute and long-term-care costs are counted, 30% of disabled elderly persons have catastrophic costs.[10] Many of these persons "spend down" their assets to qualify for Medicaid payments for nursing home care.

*See also the editorial by K. J. Mahoney, PhD, and M. R. Meiners, PhD, "Private *and* Social Insurance—The Feasible Option," on pages 74-76.

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Out-of-pocket expenses for health care paid by the elderly were about 17% of after-tax income in 1991. A third of these expenses went for nursing home costs.[11] For poor, minority, and female elders and those living alone, health costs are an even greater proportion of income. Single older women living alone may spend as much as 42% of their income for health care, including long-term care.[12] For the institutionalized elderly, expenditures for long-term care include not only medical care, but food and shelter as well.

Medicaid (42%) and direct out-of-pocket payments by patients and their families (43%) are the main sources of financing for long-term care.[8] The United States spent about $60 billion on long-term care in 1989, including $48 billion on nursing home care.[13] The average cost of nursing home care is $23,000 a year per patient.[8] Aggregate spending on nursing home and home health care is expected to double or triple from 1990 to 2040.[14,15]

A better system must be developed to finance long-term care. An excessive financial burden is placed on the individual at the time of service. A consensus has developed that insurance must be used to pay for long-term care, but experts disagree on whether it should be financed by private insurance, through a public-private partnership, or within the public sector.

Private Insurance

American private health insurance, as initially offered by Blue Cross in the 1930s and later by Blue Shield, was based on community rating—charging all subscribers the same premium regardless of the risk of illness. Currently an increasing proportion of private insurance plans (commercial and nonprofit) charge higher premiums for those at greater risk of contracting illness—experience rating.[16] People requiring or likely to require long-term care are placed in serious jeopardy by experience-rated private health insurance: if they can obtain insurance at all, they must pay more than younger people even though their average income is likely to be less—only 62% that of the general population.[3] Given these realities, the private financing of long-term care presents difficulties for both private insurers and for those needing insurance.

Problems for Private Insurers

To survive financially, private insurance firms must have the capacity to predict the health care costs of different groups.[17] Calculating costs is a problem because the need for long-term care may not occur until 20 years or more after the insurance is purchased.[8,18]

Serious disability for the elderly, especially for those older than 85, is a common and often costly event, thus making insurance for long-term health care difficult to market. Premiums must be high enough to cover costs, but low enough to attract clients.[17]

To insure a large number of people at reasonable rates, insurers must attract the younger employed population. The market for long-term-care insurance consists of persons older than 65 whose age places them at higher risk and heightens their urgency for insurance coverage, and younger healthy groups that might obtain long-term-care insurance through employment. Severely disabled persons younger than 65, many of whom are on Medicaid, belong to neither market because they are generally uninsurable.

The younger market is small, comprising in June 1990 only 5% of all long-term-care policies.[19] Insurance offerings to younger healthy groups through employers have attracted little interest among young workers for whom the prospects of long-term disability are remote.[20(p115)] By mid-1990, only 150 employers in the United States had agreed to offer long-term-care plans, and when offered such policies on an employee-pay-all basis, only 5.2% of employees elected to enroll.[21]

There are numerous and serious impediments to expanding the younger market for private insurance for long-term care. Few employers wish to involve themselves in this type of insurance; they have enough difficulties with the cost of health insurance.[8] Employees have more pressing financial needs than insurance coverage of which benefits are decades away. Although premiums in the young market are low, benefits shrink with inflation.[22] In 30 or 40 years, nursing home daily rates will exceed $200, meaning that a 20-day deductible would translate into $4,000 in out-of-pocket payments for the first three months of a nursing home stay[14]; it is doubtful that income and assets in today's economy will grow fast enough to make such payments widely affordable.

Unless insurance for long-term care is made compulsory, younger persons are not likely to purchase this product in large numbers, thereby leaving insurers the difficult task of marketing high-cost policies to high-risk elderly persons.

Only 1.65 million private insurance policies for long-term care were in force in 1990.[19] Although the insurance industry points to a recent increase in the number of policies, this growth is concentrated among healthier and wealthier customers.[23] The insurance industry admits that 58% of persons older than 65 cannot afford long-term-care insurance.[21] Even as the number of policies grows, the number of people needing this insurance is also increasing; between 1990 and 2030, the number of people requiring assistance with activities of daily living may almost double.[8]

Problems for Consumers

The high cost of premiums price many people out of the long-term-care insurance market. Even those who can afford such policies may be unable to renew their coverage. Whereas policies generally claim to have a premium that does not increase with age, companies can raise rates as long as they do so for broad categories of policyholders.[24] In 1990, the average annual premium for $80 of nursing home benefits a day, with a 20-day deductible and inflation protection, was $1,395 at age 65, rising to $4,199 at age 79.[19] Half of elderly couples live on less than $20,000 per year.[24] If a couple older than 65 at the $20,000 income level purchased low-cost policies for $2,000 ($1,000 for each person), their long-term-care in-

surance would account for 10% of their income. Long-term-care policies whose premiums exceed 5% of income are considered unaffordable.[8] By that criterion, couples older than 65 would need to earn $40,000 or more to be able to purchase this coverage; only 18% of elderly couples earn above that amount. The US General Accounting Office found that long-term-care insurance affordability exists for 20% of the 65- to 79-years age group.[25]

Cohen and associates, principals in LifePlans Inc, contend that the pool of potential purchasers of private long-term-care insurance reaches as high as 50% of persons aged 65 to 74 years.[23,26] Their estimates are based on purchasers of private insurance and cannot be generalized to the national population.[27] In contrast, other studies including those of the Brookings Institution and the Employee Benefits Research Institute, using US Census Bureau population surveys and other nationally representative databases, found that only 10% to 20% of the elderly can afford private long-term-care insurance and that approximately 5% of income is available to purchase this insurance.[24,28-31]

Is the limited affordability of private long-term-care insurance mitigated by the availability of Medicaid? Medicaid eligibility is restricted to those who meet a stringent means test or for those whose assets have been depleted by costs for long-term care. Moreover, because Medicaid reimbursement rates are low, many nursing homes refuse Medicaid patients, thereby creating a two-class system of long-term care.[28]

Individually paid premiums are a regressive way to provide long-term-care protection; as a flat dollar amount, a premium represents a greater burden on lower-income people than on the well-to-do.

People with illness or a high risk of illness may be denied coverage. According to a study published by the Health Insurance Association of America, 15% of the elderly have disabilities that cause them to be rejected for long-term-care insurance.[21] Some companies have rejection rates of 30%.[24]

To protect themselves from catastrophic losses, private insurers sell long-term-care policies with limited benefits. Most private policies specify that a policyholder must be dependent in three or more activities of daily living before receiving benefits for home health services.[14] Less than 10% of the population younger than 85 and less than 30% older than 85 have impairment that is considered severe disability under this definition.[17] Yet, many persons with fewer than three impairments to daily living need long-term-care services.[3]

Long-term-care policies generally pay a fixed fee rather than reimbursing actual charges, with most policies paying between $50 and $100 for a nursing home day. About 70% of policies have optional inflation protection, generally increasing benefits at 5% a year; such protection will likely be inadequate because from 1965 to 1990, nursing home costs have inflated at an average rate of 10% a year and home health care costs at 9.5% a year.[32] Although inflation protection generally increases premiums by about 25%,[14] the added premium cost can reach 90%.[32] Nursing home deductibles range from 0 to 100 days. A typical policy provides $50 a day after a 20-day deductible. Assuming the daily cost to be $80, a year's stay would require an out-of-pocket expenditure of $11,950 over and above payment of the insurance premium.

Maximum benefit periods, often four or five years, limit the duration of care, and some policies have a maximum lifetime payout. Although most policies are guaranteed renewable, companies can evade this guarantee by dropping an entire class of policyholders.[24]

The market price of private long-term-care insurance is out of reach for many of its potential customers. In this sense, universal commercial long-term-care insurance, as the market is currently structured, is unworkable for both the insurance industry and health consumers.

Public-Private Partnerships

Some may argue that the solution to long-term-care coverage is a public-private partnership.[33] The most prominent proposal for such a partnership is the series of Robert Wood Johnson Foundation demonstration projects funded in eight states. These demonstrations encourage the marketing of private long-term-care policies by easing Medicaid eligibility for those who purchase insurance. For example, persons who purchase insurance covering two years of nursing home or home health care might become eligible for Medicaid after exhausting their private benefits and might be allowed to keep $50,000 of their assets. Under ideal conditions, everyone would gain from this plan: policyholders would receive public assistance without having to spend themselves into poverty; insurers could market policies whose lower maximum benefits might make them more affordable; and the state might reduce its Medicaid costs because persons requiring less than two years of long-term care would be kept off the Medicaid rolls. The insurance policies would be required to conform to the National Association of Insurance Commissioners model guidelines, including coverage for Alzheimer's disease, policy renewability, and preexisting illness restrictions limited to six months.[34]

Four states—Connecticut, Indiana, New York, and California—are in various stages of implementing this public-private partnership. In New York State, people who buy a state-approved private long-term-care policy could become Medicaid-eligible while keeping their assets after three years of private coverage. Private policies would provide at least $100 per day for nursing homes and $50 per day for home care, with an inflation protection clause. Annual premiums are estimated at $1,500 to $2,000 if purchased at age 65. New York State projections are that elderly couples would need at least $20,000 in annual income to afford these policies, but consumer advocates counter that the policies would be unaffordable for many people at the $20,000 income level ("Medicaid Plan Promotes Nursing Home Insurance," *The New York Times*, May 3, 1992, p 1).

The flaw in the public-private partnership is that out-of-pocket costs—premiums, deductibles, and uncovered

expenses—remain beyond the reach of many middle-income persons.[9] A US General Accounting Office report has warned that under such public-private partnerships, state governments would be called on to provide Medicaid benefits for upper-income people who might otherwise not qualify for Medicaid, which could add to Medicaid rolls and hence to overall Medicaid costs. The report concluded that such programs could become subsidies for the wealthy—who could protect their assets through Medicaid—without making long-term-care coverage affordable to middle-income people.[25]

Another mechanism to encourage public-private partnership is government subsidy—through tax credits or vouchers—to assist families with the purchase of private long-term-care insurance. But if the subsidies are insufficient, millions of Americans would be unable to purchase private policies even with government assistance; if the subsidies are generous, they would substantially increase taxpayer costs.[24] Because private insurance is burdened with administrative and marketing costs of about 12% compared with 3% for Medicare and Medicaid,[35] a government subsidy program would be more costly for the amount of private insurance provided than either Medicaid or publicly financed insurance. Expanding private long-term-care insurance will not substantially reduce the need for public funding. Rivlin and Wiener reported that for the periods 1986 to 1990 and 2016 to 2020, even a major expansion of private long-term-care insurance would result in small projected savings for Medicaid and Medicare of 1% and 6%, respectively.[28] The subsidies to the private sector would reduce tax revenues that finance programs such as Medicaid that assist lower-income groups; yet they would tend to benefit higher-income people who can afford subsidized private insurance.[28,36]

The public-private partnership relies on private insurers who are attempting to survive in a competitive system and will thus encounter a familiar potpourri of problems: companies marketing only to groups judged to be lower risks, benefit packages with high deductibles and copayments, fixed-payment plans with inadequate inflation protection, experience rating, and premiums that pose serious barriers to those with lower incomes.[18,36] State regulation of long-term-care insurance practices has thus far proved to be inadequate.[37]

A public-private partnership with many competing insurers is not structurally designed to control costs and is likely to replicate for the long-term-care sector the "runaway inflation that accompanied the expansion of hospital insurance."[18(p26)] Even if states are able to control the Medicaid contribution to long-term care, containing the private insurance portion of the program's costs will be difficult. In the mixed public-private health sector of the United States economy, 11 serious cost-control measures introduced during the past two decades have been unable to stop the growth in national health care expenditures.[38] According to Davis and associates,[39(pp1,3)]

> Attempts to curb rising costs . . . have been sporadic and, with a few notable exceptions, largely unsuccessful. . . . These efforts, which have surfaced with stunning speed in the early 1980s, are fragmented and lack any cohesive guiding policy. . . . Rather than respond to financial incentives by improving productivity and efficiency, eliminating marginally beneficial services, or curbing excess managerial and professional salaries or profits, providers may simply refuse to see charity patients, [and] discriminate against less profitable patients, such as those frail elderly who require extensive nursing assistance or have complicating conditions. . . .

Over the past 10 to 15 years, nations in the Organization of Economic Cooperation and Development have shown that public financing with global expenditure caps or limits on fees paid to providers are the most effective methods for controlling costs.[40] Without cost control, the public-private partnership is likely to experience over time the erosion of access to long-term care—with the greatest effect on the low-income elderly—that inevitably accompanies rising costs.

Social Insurance

Social insurance—often combining social security and tax revenues—is a popular approach to funding health care in Western Europe and underlies the Medicare program in the United States.[40] Because coverage is compulsory, social insurance spreads the financial risk of illness among the entire population or at least among the working population.

Under social insurance, as exemplified by the US Social Security program, a large proportion of the population is placed together in a single risk pool. Contributions are compulsory and are earmarked so that everyone who contributes is eligible for benefits.[41] Social insurance for long-term care bases its payment structure on the ability to pay—whether through social security or income tax financing—by which lower-income persons and those with more severe disability receive more benefits for less cost to themselves. Lower-income families tend to receive somewhat greater benefits in relation to their level of contributions than those with higher incomes. Most important, social insurance represents a transfer of income from younger employed people to older retired persons or to those who become prematurely disabled; in that sense, social insurance is in the individual self-interest of contributors, most of whom will require its benefits as they grow older. To protect younger generations from paying excessively to finance long-term care for those currently older than 65, a new social insurance program should be phased in gradually and should require people older than 65 to contribute.

Market failure for private retirement pensions made necessary the enactment of the Social Security Act of 1935. Given the limited affordability of private long-term-care policies, we predict that market failure of private long-term-care insurance will lead to the development of social insurance in the 1990s. Public insurance ensures that equitable protection and coverage will be provided for the entire population; that long-term care will be experienced as an earned benefit rather than as a welfare handout; because there is equality, there will be broad support for maintaining and improving the program; the problems of "adverse selection" disappear because there is no need to screen out adverse risks; and with financing

through earmarked payments, everyone contributes and the risk is spread across the entire population.[24]

Social insurance for long-term care does create one potential problem: because all disabled people would be covered for health, housing, transportation, and other support services, family members currently providing high-quality care in the home without pay might be replaced by paid caregivers, thereby increasing costs. Harrington and co-workers described a program in which family members who are caregivers would be paid for the services they provide with the hope that such reimbursement would allow more disabled people to remain at home rather than enter expensive nursing homes. Utilization and costs would be controlled through global budgeting and case management.[42]

Political Feasibility

Supporters of the public-private partnership generally cite one reason for failing to embrace public long-term-care insurance: fear of imposing new taxes or of further straining government deficits.[6,14,33] The flaw in this reasoning is that dollars spent on long-term-care insurance premiums can empty taxpayers' wallets as fast or faster than dollars generated through taxes or social security payments. The social insurance approach to long-term-care financing received major political support from the prestigious Pepper Commission, and social insurance legislation has been introduced into the US Congress and several state legislatures. A growing number of national opinion polls indicate substantial support for a public long-term care plan including both the elderly and the under-65 disabled ("Poll Shows Americans Willing to Pay More for Long Term Care," *American Association of Retired Persons News*, May 3, 1993).[43]

Although public opinion favors social insurance financing for long-term care, the public has far less influence than health care professionals and insurers on US health policy.[44] The insurance and nursing home industries oppose public long-term-care insurance. Moreover, under the special-interest politics traditional in the United States, a minority of politically powerful elders with ample funds to purchase private insurance may be coopted by the promise of subsidized insurance and asset protection and may thus be reluctant to stand up for the concerns of lower-income seniors.

The political environment is increasingly ripe for health insurance reform and strong cost-containment measures. Many Americans expect the federal government, not the private sector, to lead the way.[45] Moreover, the benefits of publicly financed long-term-care insurance will become clearer with the evolution of current economic trends: the conjuncture of rising costs of long-term care and declining real family incomes.

Summary

Long-term care is inadequately financed in the United States. Should such financing be accomplished using the private insurance mechanism, relying on the public sector, or combining public and private approaches? Private insurance generally uses the principles of experience rating—that people with higher risk of illness are charged higher premiums than those with lower risk. In the area of long-term-care financing, this principle creates a dilemma for both insurers and consumers. Policies are more likely to be purchased by elderly persons who face a higher risk of needing such services than by younger persons, and premiums will be affordable for a relatively small percentage of those who need policies. The public-private partnership concept is beset—in somewhat muted form—by the same difficulties. Although private long-term-care insurance and the public-private partnership can alleviate the financial suffering created by long-term-care costs for some persons, no evidence exists that these solutions, based on experience rating, can provide universal and equitable long-term care.[46] The problem is likely to worsen with more people requiring such care and the growing costs of long-term care.[15] The economic realities of long-term care and growing consumer support for publicly financed solutions have set the stage for broad public acceptance of social insurance for long-term care.

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Commentary

Dysfunctional Doctour of Physik

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At the very least, the medical profession today is experiencing change and inordinate stress. I hear the words dissatisfied, disappointed, disillusioned, disturbed, distressed, and disgusted in physicians' conversation with their peers, and see these words in correspondence I receive on the state of medicine. As something of a diversion from this distress, in my later years I have returned to literature, the same literature that I skipped during my school days. Reading the classics at this time gives me a different perspective, free from earlier predetermined notions and without the point of view of class requirements or the instruction of a professor. Illness and medicine, I discover, play a surprisingly large role in the characterizations and events in novels, stories, and plays. I was initially disturbed that the image portrayed of the profession by authors over the centuries is not exactly heroic. In fact, many physicians are the object of scorn and ridicule or at least unsympathetic characterization. Even their good work is treated differently than what might be expected, with a display of ambivalence, often in the same work. That medicine is in a transition from what appeared to be overwhelming acceptance and support to one of doubt and criticism is obvious. That physicians are the subject of criticism is not new. When we say to each other, "What has gone wrong?" I contend, "Not much."

In the ninth century, in the midst of the great Islamic Renaissance, al-Ruhawi wrote in *Adab al-Tabib*, or *Practical Medical Ethics*:

> There is no doubt that good and virtuous people are obligated to the group of good and great physicians. He who upbraids them, blames them, and denies their rights, denies the good will of Allah, and despises His grace. There is no doubt that he who does this despises himself. The evidence of this is that when we see that he is sick, he does not go to his mother, father, or beg a favor of a friend or relation, but he asks the succor of Allah and of the physician. Then, when he is saved from his illness, he blames the physician and betrays his confidence. Such a person must not be reckoned among those who are described with reason but as a beast. How many people hate physicians and execrate them instead of loving and respecting them since they hold back from their desires and warn them not to follow their pleasures. For this reason, they dislike to be together with them in an assemblage, curse them, and always respect those who follow their desires, flatter them, and those who stoop to their rank.

Al-Ruhawi's comments are certainly the voice of experience in dealing with illness and human nature. Avicenna (980-1037), the greatest of medieval Islamic physicians who wrote the *Canon of Medicine*, which was the standard textbook of medicine in Europe well into the 19th century, was admired and respected, yet he excited jealousies and enemies who bitterly attacked the great physician. Avicenna replied:

> They cannot abide my being a physician of merit, it is painful for them to see my merits beside their ignorance. They believe they can hurt me with their slander and calumny, but their slanders and calumnies remind me of a goat who strikes the mountains with his horns.

Chaucer's 14th-century Doctour of Physik, a character told in only a few lines in *The Canterbury Tales*, is exceeded in complexity only by the Wife of Bath. Medieval scholar Walter C. Curry says, "He is a cold-blooded rationalist, moreover, a strictly scientific man who boasts that his study is but little upon the Bible." John of Burgundy, one of the most prominent physicians of the times, may have been the basis of Chaucer's character. The Doctour of Physik is Chaucer's exponent of medieval science; by the doctor's own estimate of his own abilities, one wonders whether he is sincere with his patients and whether his learning is as broad and accurate as he would have it appear:

> For the good Doctour I suspect talks too much. He is exceedingly, though perhaps not abnormally, well pleased with himself and with his profession, and seems determined that the Canterbury Pilgrims shall be properly impressed with himself and with his profession, and seems determined by his success in the recent pestilences . . . that he discourses rather ostentatiously upon the occult philosophy of medicine. . . .

The Doctour of Physik cites the names of 15 famous Greek, Arabian, and contemporary physicians whose names "roll impressively from his tongue as if they were selected on the spur of the moment and at random from a much larger reading list." In addition, he is a good businessman and by his appearance and dress, is inordinately proud. A contemporary of Chaucer's, John of Salisbury, says:

> They [physicians] soon return from college full of flimsy theories to practice what they have learned. Galen and Hippocrates are continually in their mouths. They speak of aphorisms on every subject, and make their hearers stare at their long, unknown, and high-sounding words. The good people believe that they can do anything because they pretend to all things: When I hear them talk I fancy they can raise the dead. . . . They have only two maxims which they never violate: Never mind the poor; never refuse money from the rich.

Curry suspects that the Doctour of Physik is something of a humbug in league with his apothecaries to "fleece the public." He concludes:

(Smith RD: Dysfunctional doctour of physik. West J Med 1994; 160:70-72)

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We cannot be absolutely sure about anything in the Doctor's character. Chaucer has created him so. And it is this very uncertainty as to his honesty, his honor, his sincerity, and his learning which lends a certain life-like complexity to his character and actions; it is this human contradictoriness which the author—doubtless with much twinkling of eyes and thrusting of tongue in cheek—seizes upon and develops by suggestion. The result is not merely a description of any particular man or of a professional type, but a work of art—that very human and complex Doctor of Physic himself.

Even though medicine today is far removed from that of the days of Chaucer, the character traits of the physician are amazingly similar to the criticism leveled at the profession today. A few centuries later, Shakespeare's physicians were anything but heroic and often were objects of satire even though Shakespeare was well versed in the arts and sciences of medicine.

More recently Tobias Smollett's (1721-1771) egocentric Dr Mackshane in *The Adventures of Roderick Random* insists that an injured sailor requires an amputation after a serious injury. The physician, ridiculed by the crew, is made to appear incompetent when the crew demands treatment with bandages and splints, which they administer. When the sailor recovers, "We had the satisfaction of not only preserving the fellow's leg, but of rendering the doctor contemptible among the ship's company."

In Hawthorne's short story "Rappaccini's Daughter" (1846), Dr Rappaccini is described as "a tall, emaciated, sallow, and sickly-looking man, dressed in a scholar's garb of black . . . a face singularly marked with intellect and cultivation, but which could never even in his more youthful days, have expressed much warmth of heart," with an "infirm voice of a person affected with inward disease," and further noted to be "the sickly and thought-worn Doctor." His rival at the school of medicine, Dr Baglioni, says of Dr Rappaccini:

. . . he cares infinitely more for science than for mankind. His patients are interesting to him only as subjects for some new experiment. He would sacrifice human life, his own among the rest, or whatever else was dearest to him, for the sake of adding so much as a grain of mustard-seed to the great heap of his accumulated knowledge.

He was singular, or myopic as is said today, in his interests; his daughter who tends his extensive garden where he raises poisonous plants says, "This garden is his world." Baglioni warns that Rappaccini would sacrifice his own beautiful daughter "as the victim of his insane zeal for science. For—let us do him justice—he is as true a man of science as ever distilled his own heart in an alembic." He cautions the young medical student to beware: "Rappaccini, with what he calls the interest of science before his eyes, will hesitate at nothing." The chilling tale of the evil, sinister doctor in the objective cause of science leads to the death of his own daughter.

The history of medicine is full of glowing accounts of the triumphant march of new discoveries and treatments as well as the heroic accomplishments of physicians who were often described as demigods, but not so the physicians in the works by the authors of the day. Ralph Major allows, however, that Baron Guillaume Dupuytren (1777-1835) was "the first of surgeons and the last of men." For instance, in the 19th century, the disjunction in the assessment of the medical profession may be illustrated by Sir William Osler's remarks in 1901 on medical progress of the previous century—The Age of Science:

For countless generations the prophets and kings of humanity have desired to see the things which men have seen, and to hear the things which men have heard in the course of the wonderful nineteenth century . . . at last Science emptied upon him from the horn of Amalthea blessings which cannot be enumerated, blessings which have made the century forever memorable; and which have followed each other with a rapidity so bewildering that we know not what next to expect . . . there is no one measure which can compare with the decrease of physical suffering in man, woman, and child when stricken by disease or accident. . . . This is the Promethean gift of the century to man.

The actual practice of medicine in America was portrayed more realistically by Herman Melville in *The Confidence-Man* (1857) in the dispute between the "herb doctors," especially the movement of Samuel Thomson (1769-1843), and the regular "mineral doctors" who were practitioners of "heroic medicine," purging with calomel advocated by Benjamin Rush (1745-1813). In Melville's earlier novel, *White Jacket: or The World in a Man-of-War* (1850), Fleet Surgeon Cadwallader Cuticle, a small, withered man, was "an enthusiastic in his calling . . . untouched by the keenest misery coming under a fleet surgeon's eye" and "seemingly impervious to the ordinary emotions of humanity," yet he could not be considered cruel-hearted. By stretching the indications for surgery, Cuticle performs an amputation on a sailor who had been shot: "The withered, shrunken, one-eyed, toothless, hairless Cuticle; with a trunk half dead—a *memento mori* to behold" stands in the role of the "Regenerator of life." Although Surgeon Cuticle is familiar with and cites the most famous surgeons of the day: Charles Bell, Benjamin Brodie, and Dominique Larrey, his patient dies immediately after the operation. Cuticle is a venerable practitioner, but he is not spared criticism, becoming the object of biting satire. In Melville's Civil War poem, "A Scout Toward Aldie," he was greatly sympathetic: "This surgeon was the kindliest man/That ever a callous trade professed."

Anthony Trollope's novel *Doctor Thorne* (1858) chronicles the competition between Thorne and his rival, who was dubbed satirically Dr Fillgrave. Thorne was not quarrelsome, but "there was that in him which would allow him to yield to no attack," as he carried on a running feud with his professional rival. With a slovenly manner, he was a poor man: "The gift of saving money had not been his." The wealthy families of Barsetshire capriciously dismissed the one doctor to call in the other, which Dr Fillgrave relished "like a prize taken from the enemy." Although Thorne is the trusted adviser of a dying wealthy man, he can hardly be considered a meliorative character.

In George Eliot's *Middlemarch* (1871-1872), a classic of 19th-century literature, Tertius Lydgate, a new young physician, is one of the most important characters in the novel. He receives this comment from one of the people of Middlemarch, a mythical village in the midlands of England: "For my own part, I like a medical man more on a footing with the servants; they are often all the cleverer. I found poor [Doctor] Hick's judgement unfailing; I never

knew him wrong. He was coarse and butcher-like, but he knew my constitution." After calling in Lydgate to attend a member of the household, the mayor makes a familiar charge against the profession, saying, ". . . this is beyond a joke. To let a fever get unawares into a house like this. There are some things that ought to be actionable, and are not so—that's my opinion." One of the ladies of the town, talking to Lydgate's fiancee, says:

> Mr Lydgate is very intellectual and clever; I know there is an attraction in that. I like talking to such men myself; and your uncle finds him very useful. But the profession is a poor one here. To be sure, this life is not everything; but it is seldom a medical man has true religious views—there is so much pride of intellect. And you are not fit to marry a poor man.

Yet, Eliot comes to the aid of the doctor when Dorothea says:

> Mr Lydgate would understand that if his friends hear a calumny about him their first wish must be to justify. What do we live for, if it is not to make life less difficult to each other? I cannot be indifferent to the troubles of a man who advised me in *my* trouble, and attended me in my illness.

Lydgate eventually becomes a successful practitioner in London, although he considered himself a failure for not having succeeded in Middlemarch.

More recently, in Marcel Proust's great work, *A la Recherche du Temps Perdu,* published between 1913 and 1927, style and fashion were everything. The character of Dr Cottard was the subject of considerable debate: the boorishness and vulgarity of the physician and his wife were a source of scorn by their fashionable social class. The doctor's demeanor was "a shell of coldness, disdain, gravity . . . conscious that he was often boring," which amused the fashionable Verdurins. When the author was sick, his mother called in Cottard. His mother disagreed with Cottard's treatment; not until they followed the prescribed treatment did he recover: "and we realized that this imbecile was a clinical genius." Although lacking in social graces, Mme Verdurin defends Cottard after he saved her husband "when the whole faculty had given him up" and says, "I don't call him Doctor Cottard, I call him Doctor God!" Cottard was promoted to professor at the university; although he had been honored, which satisfied his vanity, he never became cultured, and thus did not belong in the social strata he had entered by virtue of being a physician. Proust was current in his criticism of medicine, saying, "Nature hardly seems capable of giving us any but quite short illnesses. But medicine has annexed to itself the art of prolonging them."

These examples may not represent a statistically significant sampling of physicians in literature, yet the theme of criticism, or at the least ambivalence, toward the medical profession extends to the remote past. Few sympathetic characterizations of physicians come to my attention—Mark Twain's doctor in *The Adventures of Huckleberry Finn* (1884) is a notable exception. The hubris of the self-congratulating physician, stretching the indications for surgery, intimations of overpaid as well as poorly paid physicians, the ineptitude of some practitioners, and the portrayal of the evil doctor make up the character of some of the physicians of literature.

The intrusion of "third parties," bureaucracy, and regulation that has created more and more stress on physicians today leads the modern physician to yearn for the "good old days." Surely things are not what they used to be. I conclude, they never were. Melville appositely says, ". . . take mankind in mass, and for the most part, they seem a mob of unnecessary duplicates, both contemporary and hereditary," which seems to be the way politicians, the press, and insurers view the mass of medical "consumers"; yet Melville also says, ". . . take high abstract man alone; and he seems a wonder, a grandeur, and a woe," which is the way physicians see each patient—and that, concisely, is the conflict.

For years I have thought nothing could be more useless than the pursuit of literature while my contemporaries were becoming proficient at golf or real estate or many other activities that seemed to have some tangible benefit. By discovering through the perspective of literature that what we are experiencing is the rule rather than the exception, I think I have been able to withstand the onslaught of criticism somewhat better than otherwise. If, from this survey, anything is amiss, it is the unprecedented sanction and support that medicine received during the middle decades of the 20th century, which, to me, is eccentric to literature's physicians. Today's physician, though relying little on the theories of the Doctour of Physik, such as the humors and stellar influences, has more in common with the medieval physician than one might wish to admit. The criticism and withdrawal of support has occurred as abruptly and as coldly as for any of literature's surgeons. We may not have the confidence of Avicenna that our critics are butting their heads against a mountain, nor that the edifice of medicine has the durability of the Rockies, yet the profession will somehow endure.

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Editorials

The Coming of Age of Performing Arts Medicine

In 1989 a review appeared in *The New England Journal of Medicine* describing the medical problems that occur in performing musicians.[1] In providing an editorial comment to that review, I suggested that this relatively new field of medicine might be coming of age.[2] In this issue of *The Western Journal of Medicine*, Ostwald and colleagues provide a comprehensive survey of the broader field of performing arts medicine.[3] The abundant information that they have eloquently summarized does indeed support the idea that performing arts medicine has reached maturity.

Certainly the field has continued to grow as more physicians and other health care professionals are expressing interest in performing arts medicine. A professional organization, the Performing Arts Medicine Association, was established by a group of physicians in 1989, and its membership is steadily expanding, now including nonphysicians as well. New performing arts medicine clinics and groups have been organized in various cities, both in the United States and abroad, many encompassing the many disciplines called for by Ostwald and co-workers. In some countries, including the United Kingdom, there have been requests for national initiatives to tackle the important issues regarding health care for performing artists.[4] A textbook of performing arts medicine has appeared,[5] and another, to be published in German, is currently in preparation. The journal, *Medical Problems of Performing Artists*, has thrived as a repository of information relevant to the field, as is evidenced by the number of references to that journal in the article by Ostwald and associates. Another publication with a somewhat different focus and slant, the *International Arts Medicine Journal*, has more recently appeared on the scene.

Meetings and symposia on various aspects of performing arts medicine—sponsored by health care institutions, schools, and performing arts groups—are bringing the concept of arts medicine to a much wider audience. Several professional medical societies have formed special interest groups or sections in performing arts medicine, and seminars or workshops on various topics can be found on the agenda at national meetings of these associations.

Despite all of this, we cannot be satisfied with our progress. Many—perhaps even most—physicians and other health care professionals are completely unaware of these developments. An equally substantial number of performers, including dancers, musicians, and especially those in theatrical arts, remain ignorant of the increased and specialized interest in their health problems. Many of those cognizant of the existence of these services are unable to take advantage of them because of inaccessibility. Performing arts schools and organizations, including dance companies and orchestras, even if aware of the increased attention being paid to the medical care of performers, often remain unreceptive or indifferent to dialogue and interaction. In some cases it is unclear whether this represents inertia, the fear of promoting the development (or simply the admission) of problems, or active disinterest and antagonism. A large number of performers, especially students, young professionals, freelancers, and members of small ensembles, are unable to obtain specialized services, either because of their location or because of financial limitations. Even for members of orchestras or companies with comprehensive health care plans, the limited number of arts medicine practitioners may not be on the list of acceptable providers.

There is little evidence that the development of performing arts medicine has had any effect on methods of teaching, on the playing, practicing, or dancing habits of performing artists, or on the incidence of performance-related problems. In my own practice, I see indications of this repeatedly. Over the past 14 years there has been no decrease among my patients in the duration of symptoms from onset to the initial medical consultation (the mean is still 30 months), suggesting that seeking professional advice from physicians, or indeed other health care providers, remains relatively low on the list of options considered by performers.

Performing arts medicine has much work to accomplish. An enormous number of questions remain unanswered regarding the mechanisms, contributing factors, and methods of management of even the most common disorders. There is even little agreement on the diagnostic terms used to describe these problems. For instance, the trunk and arm pain so commonly experienced by instrumentalists may be characterized as overuse, tendinitis, cumulative trauma disorder, repetitive motion disorder, occupational cervicobrachial disorder, or regional pain syndrome. The pain may be attributed to inflammation, strain, or sprain; a clinician may localize the disorder to tendon, muscle, nerve, or connective tissues. Regarding the mechanism, some would focus on ergonomics, considering the static and dynamic loads associated with a particular activity. Is the problem one of excessive playing, faulty technique, or both? Is it caused only by stress? Or is it entirely attributable to hysteria or even feigned?

Performing artists are understandably bewildered by the array of practitioners offering advice and help. Does a performer see a teacher, coach, physical therapist, massage therapist, Alexander or Feldenkrais instructor, psychologist, or physician? The treatment suggested may include relative rest or total abstinence, exercise, the modification of posture, medications, massage, manipulation, change in diet, technical alterations, relaxation technique, stress management, injections, or even surgical therapy. Any of these at some time may be useful and even necessary, but the potential for confusion and conflict is obvious, especially when one of these approaches is touted as "the only way."

Where does performing arts medicine go from here? I could not agree more with the suggestion of Ostwald and colleagues that a multidisciplinary and collaborative approach to the problems of performing artists is not only desirable but absolutely necessary. Education must be the most important focus of attention for physicians in performing arts medicine. Physicians need to educate themselves and their colleagues regarding the progress that has been made and what is currently available. They need to learn more about the mechanics involved in the various types of performance in which patients are involved. Even more, physicians need to understand what drives and motivates performers and performing arts students.

It has been popular to compare performing arts medicine with sports medicine and to assume that skill in one field automatically applies to the other. Although there are obviously similarities both in the types of disorders seen and in the methods of treatment, there are a number of differences as well. Performing artists are not athletes, and to approach them with the same mind set is to court disaster. Most physicians practicing performing arts medicine have developed whatever skills they may have by seeing a large number of performer-patients, by discussing issues with colleagues in various disciplines, medical and musical, and to some extent by trial-and-error approaches to treatment. A sufficient body of knowledge has now accumulated to begin developing training programs for interested physicians. There are many problems to surmount. It seems feasible at this point to offer elective time during or after formal residencies or fellowships in selected recognized specialties, but ultimately a program that provides exposure to several relevant disciplines should be made available. The Performing Arts Medicine Association would be the logical group to spearhead this effort.

Of equal importance is communicating information about performing arts medicine to the performers themselves and to their instructors at all levels. Particularly critical is the need to inform those who teach the very young, where the seeds of future playing-related problems are almost certainly germinated. We should encourage teachers to incorporate physiologic principles into the techniques used in playing, singing, or dancing. What can also be taught is how to approach learning a performing art, such as techniques of practicing, the importance of variation during practice sessions, avoiding the endless repetition of a series of movements, and the usefulness of mental preparation and learning away from the instrument or the dance floor. We can also make a contribution at the level of a conservatory or school. Instruction in the physical limitations of the musculoskeletal system, how to recognize the warning signs of impending physical or emotional problems, and principles of conditioning could all be incorporated into the curriculum.

There is a need to interest far more basic and clinical scientists in the unsolved problems of performing arts medicine. The mechanisms of development and the best methods of treating the muscle pain syndromes and occupational cramps that afflict performers are but two of the many urgent areas awaiting elucidation by the application of rigorous investigative methods. The technology exists to answer those important questions.

Coming of age generally requires the assumption of additional responsibility. Performing arts medicine is a field that has evolved out of the perceived need for specialized care for musicians, dancers, and other performers. We must solidify its foundations by expanding the knowledge base of information on the cause and treatment of performance-related disorders. We need to interest young physicians in the field and to develop programs to train them in its many aspects. Most important, we have to communicate what we have learned to the performing artists and their teachers to ensure that all who wish to avail themselves of these services can do so.

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Private *and* Social Insurance—The Feasible Option

THE RECENTLY RELEASED Clinton Health Plan (September 1993) drives home a number of thought-provoking insights regarding the future financing of long-term care. It also provides a critique of the feasibility of a universal social insurance program such as that proposed by Estes and Bodenheimer in this issue of the journal.[1]

The first lesson to be obtained from the proposed health plan is that a social insurance approach to long-term care is expensive. Of the $83 billion a year the Clinton Health Plan proposes for new public spending (once the program is fully operational), approximately $25 billion is devoted to a social insurance for long-term care, and that initial annual expenditure of $25 billion (based on full funding) provides only a dollar-limited amount of home- and community-based care for the most severely impaired persons.

Part of the reason even a limited social insurance program is so expensive is that a substantial portion of the total expenditures go to persons who can afford to insure themselves.[2] But even the incremental costs can be large and unpredictable in light of the high probability of induced demand. This is why the Clinton Plan had to include a "capped entitlement."

Ball captured the importance of these cost arguments: "The main policy and political problem, however, is putting the very large total costs on the government. The social insurance plan has to raise enough money to meet the total costs, not just the incremental costs, and it would have to do this in the face of many other important social needs."[3(p159)]

And that is the second lesson. The financing of long-term care is a major issue on the public agenda, but there are other competing priorities. The events of the spring and summer of 1993 provide an excellent case study of this point. The release of the Clinton Health Plan was delayed while the Congress debated proposals to reduce the budget deficit and spur the economy. The Budget Reconciliation Act of 1993 included one of the largest tax increases in history and depleted many of the revenue sources slated for health care reform. The health plan itself faced competing pressures to provide coverage for the uninsured while adding new benefits such as prescription drugs and mental health services for everyone. In the end, the long-term-care benefits of the Clinton Plan are limited in scope, and eligibility has been restricted to the same frail group Estes and Bodenheimer fault some private insurers for focusing on.

In interpreting what happened, it is useful to reflect on parallel conclusions drawn from public opinion polls. Meiners and McKay discovered that the American public viewed long-term care for the aged and disabled as an important problem, though not the top priority: "Programs focused on helping the most needy were preferred by 60% of the respondents. Thirty-five percent preferred a government program for all, but about a quarter of that group were not willing to pay their share of the new taxes that were estimated as necessary to cover the cost."[4(p34)] The results of a February 1993 Gallup poll conducted for the American Health Care Association are even more striking.[5] Of those surveyed, 76% felt the government should pay for nursing home care only for those who cannot afford it.

Despite Estes and Bodenheimer's strong arguments that social insurance is the only way to achieve universal coverage and an easy way to spread risks based on ability to pay, it appears unlikely that the public is willing to pay for a universal social insurance program in the foreseeable future. A recent edition of *The New York Times* summed it up this way: "Administration officials say it is neither desirable nor possible for the government to finance all long-term care" (R. Pear, "Clinton Health Proposal Includes New Program for Long-Term Care," *The New York Times*, September 8, 1993, p A15). The Clinton Health Plan, like the Pepper Commission and virtually all major congressional proposals before it, concluded that the public sector cannot go it alone.

Because neither the private nor the public sector seems capable of providing an adequate solution, a public-private partnership seems to be the only feasible alternative.[3] One such plan has been adopted in the states of California, Connecticut, and Indiana with support from the Robert Wood Johnson Foundation.[6] Those who buy a partnership policy are entitled to keep assets equal to the amount their insurance paid out and still receive Medicaid benefits. This prevents elderly persons from having to "spend down" their assets to the poverty level once the insurance policy is exhausted in order to receive Medicaid assistance.

The partnership model provides a dollar of asset protection for each dollar paid out by a state-endorsed long-term-care insurance policy. The dollar-for-dollar approach allows for a variety of product designs with benefits ranging from one year of coverage on up. This approach encourages people to plan for their long-term-care needs and allows persons of different means the option of choosing quality protection that they can afford.

Participating states have amended their Medicaid programs to protect elderly persons from impoverishment. To do this, insurance payments for long-term care are regarded as equal to asset spending to determine Medicaid eligibility. Once on Medicaid, they will be able to maintain their assets up to the amount of insurance payments. Income would still be applied toward long-term-care expenses.

The poverty protection offered by the partnership plan should be an especially strong incentive for those most at risk of depleting their resources when the need for this care arises. Middle-income elderly generally have fewer assets to protect and are least able to afford current private insurance "lifetime" policies (four years or more). They are also the most likely candidates to spend down to the poverty level to qualify for Medicaid. The extra protection offered by the partnership program makes purchasing one to three years of protection more meaningful and more affordable to middle-income elderly.

Contrary to Estes and Bodenheimer's arguments regarding public-private partnerships, these partnerships

- *Provide relatively affordable lifelong protection against the risks of long-term care.* Although premiums are age-related (the younger the purchaser, the less expensive the policy), on average, a 65-year-old person may pay an annual premium of $400 for a policy that will pay for one year of nursing home care and protect $30,000 in assets (*Wall Street Journal*, August 5, 1993, p 1).

Out-of-pocket costs are kept manageable by liberal elimination periods, a prescribed set of minimum benefits, and inflation protection. Premium payments must stop when institutional care is needed. For instance, under California's recently promulgated regulations, the elimination period for the basic policy is set at 30 days (which may be paid by Medicare for persons with acute illness); the private policy must cover at least 80% of the average cost of care (the copayments represent room and board costs, which can largely be met from present income); and inflation protection for covered benefits (5% compounded annually plus periodic upgrade offerings if inflation proves to be higher) is mandatory.

- *Provide means-sensitive assistance.* To the extent people have the means, they are expected to pay towards the cost of their care. The wealthy cannot readily receive Medicaid, as the purchaser of these special policies can only protect assets equal to insurance payouts.[7] Premiums are commensurate with the amount and duration of coverage (and asset protection) purchased. In fact, "asset protection" may be a misnomer. Poverty or independence protection may be more apt. Those who choose to take part in these partnerships will have the security of knowing that even if the worst happens—their private insurance

benefits run out and they need public assistance—they will not have to become impoverished.

It is true that only a purely social insurance can ensure universal coverage. These public-private partnerships, however, are built on the premise that the wealthy can meet their own needs; the public sector must maintain strong programs for those who are already poor or disabled, or both, and humane alternatives must be offered to people of modest means.

• *Contain Medicaid expenditures.* The fiscal impact of the partnership was estimated using the Brookings-ICF Long Term Care Financing Model.[8] Although the model is national in scope, it has been widely used to assess the effects of public and private changes to long-term-care financing.

The simulations in this model indicate that the partnership approach can yield substantial savings.[9] Medicaid was found to save an increasing amount in each period, totaling nearly a 7% drop in Medicaid's share of the total long-term care bill in the period 2016 to 2020. In addition, the share of out-of-pocket expenses is projected to drop by about 9 percentage points, with insurance paying about 16% of the total long-term care bill.

These public-private partnerships are also testing various mechanisms—including, in California, care management, preferred provider agreements, limits on insurance per diem payments, and caps on the total amount of assets any person can disregard—to help constrain overall cost growth.

• *Pioneer new product and consumer protection standards.* One goal of the Robert Wood Johnson Foundation program is to improve the quality of long-term-care insurance policies by requiring state projects to meet the National Association of Insurance Commissioners' model regulations.[7] But partnership states have gone even further, pioneering improved standards in areas including home and community-based services; inflation protection; agent training; insurer reporting; limits on future rate increases; a step down in coverage that allows persons whose financial circumstances change to lower their coverage (and premiums) without losing their insurance and without losing all of the reserves they have built up; and premium credits (for years of previous payments) when persons upgrade or replace earlier coverage.

Estes and Bodenheimer paid a lot of attention to private market failure(s). Given the newness of private long-term-care insurance and the rapid growth in sales, they may have overstated the case.[10] They also ignore the political feasibility and costs of a universal social insurance program. But, as shown here, there has also been a failure in the public policy arena. A public-private partnership of some kind appears inevitable. Partnerships such as those being demonstrated in California, Connecticut, and Indiana address some of the major reasons people have hesitated to purchase private coverage, such as affordability, confidence in standards, and adequate consumer information and education, while enhancing some of the prime motivations for purchase—access to desirable forms of care, independence, and asset preservation. Such partnerships will test how far the private sector can go and clarify the areas where only a public program will suffice. In the end, the combined efforts of the public and private sectors will be required to meet the needs of our frail elderly and disabled citizens.

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Stimulated Gracilis Neosphincter Clinical Trial

To the Editor: Fecal incontinence is a common but debilitating condition. Fortunately, many cases can be treated medically, with an adequate control of symptoms. In some patients, however, the symptoms are such that colostomy is considered. In patients in whom an anatomic separation exists in the sphincter mechanism, surgical repair gives good results, provided there is no associated neuropathy or myopathy. In patients in whom the primary disorder is a myopathy or neuropathy, current surgical procedures frequently fail. The graciloplasty, a procedure in which the gracilis muscle is transposed from the thigh to encircle the anus, leaving its vascular and neural supply intact, is one such procedure.

The gracilis is composed of type II muscle fibers, which are fast-twitch, easily fatigued fibers. The external sphincter is primarily composed of type I fibers, which are slow-twitch, fatigue-resistant fibers. This allows the external sphincter to function in a steady state of contraction.

It has been shown that low-frequency electrical stimulation of a type II muscle will convert it to a predominantly type I muscle.[1] A totally implantable generator has been developed for this purpose, and the preliminary results in England have been favorable. Williams and coworkers reported on a group of 12 patients who had intact anal sphincters and substantial incontinence for solid, liquid, and gas. Postoperatively, 9 patients were incontinent only for flatus, and 3 patients were incontinent for flatus and occasional liquid feces. No patient was incontinent for solid feces.[2]

The Food and Drug Administration has allowed clinical trials to begin in the United States, initially restricted to five institutions, to verify the results of that trial. The procedure is done in three stages. The first stage consists of a vascular-delay procedure whereby two to three vascular branches supplying the distal aspect of the gracilis muscle are divided to allow for the development of collaterals. At this stage, a diverting stoma is carried out. The second stage is performed about four weeks later. During this procedure, the graciloplasty is done and the electrical stimulator implanted so that the main nerve to the gracilis is stimulated. The conversion process is then started. The implantable stimulator is programmed during routine office visits using an external programmer. Stimulation is started with high-frequency intermittent stimulation, and this is gradually changed to continuous low-frequency stimulation. This process requires about three months. The third stage consists of stomal closure. The stimulator works continuously until such time as the patient needs to evacuate. Placing a magnet over the stimulator interrupts the stimulation, the patient evacuates, the magnet is removed, and stimulation resumes.

Using current techniques, the complication rate is acceptable. The complications specific to this procedure include muscle necrosis, lead dislodgement, infection, and rare cases of a neuralgic type of discomfort following the course of the cutaneous branch of the obturator nerve. This appears to be a self-limiting condition.

Patients suitable for the technique are those with traumatic, myopathic, or neuropathic incontinence that has been unresponsive to medical management. Also, patients who remain incontinent after having undergone pull-through procedures for congenital abnormalities are candidates. They should be psychologically stable and in reasonably good health to allow for valid long-term follow-up. If a patient suffers from the diarrheal form of the irritable bowel syndrome, this must be under good control. Patients excluded from the study include those younger than 16 years or older than 75 years of age. Also excluded are patients who have generalized neurologic disorders such as multiple sclerosis, severe arthritis, disseminated carcinoma or a short life expectancy, residual local malignant disease in the pelvis, a history of abdominal or perineal radiation, a demand cardiac pacemaker, perineal sepsis, Crohn's disease, or who demonstrate an inability to understand the nature of the procedure. Pregnancy is also a contraindication.

Physicians or patients who would like additional information about the procedure should contact me.

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Dinoprostone Cervical Gel

To the Editor: In the investigation reported by Gilson and co-workers, it was found that preinduction treatment with 0.5 mg of dinoprostone (prostaglandin E_2 [PGE_2]) given endocervically did not reduce the rate of cesarean section.[1] Indeed, the rate was more than twice as great in the treated women as in the controls, 39% compared with 16%. As noted by the authors, this finding is at variance with that of other studies. In two large registration trials conducted by Upjohn Laboratories in which the company's recently marketed Prepidil Gel (dinoprostone cervical gel, 0.5 mg) was used, there was a downward trend in the rate of cesarean delivery in PGE_2-treated patients, although the difference did not reach statistical significance.[2,3]

Of greater interest were the authors' findings of no change in the Bishop score and no difference in the interval from induction to delivery. This again is in contrast to the results obtained in studies supporting Prepidil Gel registration that clearly showed a beneficial drug effect as regards these two important indices. Although the PGE_2 used in Gilson's study was identified with the Upjohn

Company, it was in fact reformulated locally from Prostin E_2 (dinoprostone vaginal suppository, 20 mg) and placed in a methylcellulose vehicle according to the method described by Gauger.[4] Because the reformulation process results in dehydration and isomerization of PGE_2 to inactive metabolites, the interpretation of study results must be viewed critically. We suggest that the lack of demonstrable clinical benefit with the use of endocervical PGE_2 in this investigation is likely due to an unknown but reduced dosage of PGE_2 in the extemporaneous formulation.

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* * *

Dr Gilson Responds

To the Editor: We appreciate Dr Noah's interest in our article and were similarly struck by the unexpected results of our study. Nevertheless, as detailed in our metanalysis, other prospective studies have arrived at similar conclusions. We took great care that the reformulated dinoprostone we used was not altered during preparation or storage. At the time our study was carried out, Prepidil Gel (Upjohn) was not available for clinical use, and so the 20-mg vaginal suppository, Prostin E_2 (Upjohn) was used.

As noted in our article, the procedure we followed consisted of manipulating the suppository by slicing it into thin sections and allowing it to soften at room temperature for 15 minutes. The softened slices were then geometrically mixed with the contents of a 56-gram tube of sterile hydroxyethylcellulose gel, K-Y Jelly (Johnson & Johnson), to yield a homogenous mixture. Homogeneity was assured by adding a small drop of 1% methylene blue to each slice to serve as a marker. Individual doses of the mixture (0.5 mg per 1.42 ml of gel) were drawn up into plastic syringes and stored at −20°C for as long as 35 days unexposed to light. This product was removed from the freezer approximately an hour before use to allow thawing.[1,2] In a related article, cocoa butter suppositories were also used as a vehicle for the dinoprostone.[3] During the melting process in a 37°C water bath, temperatures of the molten mixture greater than 33°C resulted in aberrations in the bioactivity of the drug. We therefore avoided this vehicle and liquefaction technique.

We conclude that the short and gentle reformulation process we used is unlikely to have resulted in a loss of bioactivity or bioavailability of the active substance. It must be stressed, however, that we conducted no chemical stability tests on these extemporaneously compounded products. The current high cost of the new commercially available gel may result in the continued clinical use of such extemporaneous formulations, and so Dr Noah's comments are well taken.

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More on the Crisis in Medical Education

To the Editor: I would like to make several comments regarding the editorial by Thomas Cesario, MD, in the August 1993 issue.

First I would like to commend Cesario's thinking through of the problem of increasing demands on physicians in academic centers and the effect that this has on medical student teaching. I do not, however, understand his conclusion that cost-effective medicine precludes "good clinical judgment, effective clinical decision making, and useful clinical algorithms." We must get away from the notion that every disease with similar symptoms has to be ruled out in every patient. The incidence of diseases seen in an academic center is not in any shape or form similar to that found in the community. Bayes's theorem is applicable. Not all tests are "good" tests. Common things are common. We must teach good, cost-effective medicine. "Good" and "cost-effective" can and should be two sides of the same coin.

My second observation is that Cesario's solutions of recruiting good community physicians to teach and rewarding them are certainly not novel. Family medicine has been doing this for years. In many medical schools family physicians from the community who like to teach are given academic appointments and receive stipends and other benefits for teaching medical students in their offices. Some receive no monetary reward but do it for the love and challenge of teaching and to repay society for some of the costs of their own medical education.

My point is not to toot the horn of family medicine but to say that those of us in the academic centers need to descend from the ivory towers of academe and learn from our colleagues in other specialties. It is expensive to keep reinventing the wheel. We should look to other specialties and copy and modify their educational strategies to fit our own specialties' needs. If internal medicine had done this years ago, that specialty would not need to try to maintain three sets of faculty—clinical, research, and instructional—in medical centers.

Because most patients are not treated in medical centers, it is necessary to use the whole community as the educational arena. Students learned this and demanded it long before academicians were willing to admit it. Let's do

what the patients need—train students to treat patients, not the rare diseases seen in medical centers.

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REFERENCE

1. Cesario TC: A crisis in medical education—One person's concern (Editorial). West J Med 1993; 159:212-213

* * *

Dr Cesario Responds

To the Editor: Dr Taylor and I have no disagreement. My comment regarding clinical judgment and cost-effectiveness was made to indicate that I think they are mutually compatible. They have, in fact, similar implications merely viewed from two different perspectives—hence, opposite sides of the same coin.

Nor do I have any disagreement with the ability of family practitioners as excellent teachers and role models. I appreciate the many fine teachers who are practitioners of family medicine and am eager to include practicing physicians in our training programs because they constitute important role models for students.

I would, however, strongly disagree with the notion that internal medicine has been reinventing the wheel. We have sought to maintain standards of academic credibility and have done critical investigations when necessary to yield new knowledge on which clinical judgment or educational methods could be based.

It is not practical under the current system to suggest that many physicians can still competitively do clinical work, research, and instruction all at the same time when the competition for research dollars has become so fierce. The demands of the clinic are such now that considerable time is necessary to satisfy the expectations of practice groups and of patients. This is not to say that it is impossible for practitioners to do good research or to participate in outstanding projects. What is difficult, however, is for them to constantly maintain the funding and the support necessary to pursue the type of research that will yield essential new information to advance our understanding of the functions, the diseases, and the therapies needed to heal the human body.

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Capnocytophagal Pneumonia in a Healthy Man

To the Editor: *Capnocytophaga* species (DF-1) are facultatively anaerobic, slender gram-negative rods found as part of the oral flora. Serious capnocytophagal infections usually occur in immunocompromised patients.[1] We report a case of capnocytophagal pneumonia in an otherwise healthy young man.

Report of a Case

Malaise, sore throat, and nonproductive cough developed in a 25-year-old sailor. The patient's cough worsened, and severe paroxysms of coughing developed, followed by emesis and gasping respirations. Subsequently, he had shortness of breath at rest, fever to 38.9°C, and produced purulent sputum. On the third day of his illness, the patient was admitted to the sick bay of his ship with clinical signs of pneumonia, and empiric treatment with ceftriaxone, 1 gram every 12 hours, was initiated.

The patient was transferred to our facility four days after the onset of his illness. He appeared ill and had a temperature of 39.7°C. Bronchial breath sounds were present in the posterior basal lung fields. With the patient breathing room air, blood gas measurements showed an arterial pH of 7.48, a P_{O_2} of 50 mm of mercury, and a P_{CO_2} of 33 mm of mercury. A chest x-ray film showed diffuse interstitial and alveolar infiltrates with lower lobe predominance. Gram's stain of sputum revealed sheets of neutrophils and numerous slender, fusiform, gram-negative rods.

Therapy was initiated with the combination drug ticarcillin disodium and clavulanate potassium, 3.1 grams every four hours; tobramycin sulfate, 5 mg per kg of body weight per day; and erythromycin, 1 gram every six hours. Three sputum specimens obtained for culture during the first two days of hospital admission grew the *Capnocytophaga* species (DF-1). The *Capnocytophaga* organism was strongly β-lactamase-producing by Cefinase disc testing (BBL Cefinase, Becton Dickinson, Cockeysville, Maryland), and antibiotics were changed to the combination product ampicillin sodium and sulbactam sodium. The fever subsided over the next three days, and antibiotics were changed to an oral combination of amoxicillin and clavulanate potassium. His cough and hypoxemia resolved, and he was discharged on the fifth hospital day.

Discussion

Capnocytophaga species (DF-1) are unusual causes of infection in immunocompetent hosts. In a review of 16 cases of capnocytophagal infections in immunocompetent persons, most of the patients had serious underlying illnesses including malignancy, trauma, or surgical therapy, chronic renal insufficiency, and cholangitis.[1] Many of the patients were elderly, and multiple organisms were common. An oral source of infection was implicated in these patients.

We postulate that our patient initially had an upper respiratory tract infection, and then aspiration pneumonia developed as a complication of severe coughing spasms and posttussive emesis. Subsequently, ceftriaxone selected for the β-lactamase-producing *Capnocytophaga* species. The failure of a third-generation cephalosporin to eradicate β-lactamase-producing *Capnocytophaga ochracea* has been documented in a neutropenic patient.[2]

A recent report by Roscoe and Clarke documented the substantial frequency of β-lactamase-resistant *Capnocytophaga* species in a Canadian hospital. Of 19 isolates in their series, 6 were β-lactamase producing. Several investigators have suggested that because of the increasing frequency of β-lactamase-positive organisms, standard β-lactam agents may not be adequate therapy for oral infections in neutropenic patients.[2,3]

Our case shows that β-lactamase-producing strains can produce clinically important infection in normal hosts and should be considered in the treatment of community-acquired aspiration pneumonias. Therapy with β-lactam β-lactamase inhibitor combination agents is effective in these patients.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

The Gift of Listening

WILLIAM R. VINCENT, MD, *Pasadena, California*

Daniel was a full-term newborn infant who appeared perfectly formed and healthy at birth, but then septic shock due to group B streptococcal infection promptly developed. As he became critically ill with rapidly deteriorating lung function, he was referred for extracorporeal membrane oxygenation (ECMO) therapy. I met Daniel and his parents to evaluate him for possible underlying cardiac disease, which he did not have. After that point I no longer had any official role in his care.

I saw the parents and the infant intermittently during the next few weeks, as Daniel went through a prolonged period of receiving ECMO. When he was finally removed from the circuit, he initially appeared stable, but it soon became apparent that he had survived the shock episode only to have necrotizing bronchiolitis develop with progressive air trapping and a steadily worsening pulmonary status. Every effort to support him failed to alleviate severe pulmonary hyperinflation. Despite total parenteral nutrition, he had become a frail, emaciated, 1-month-old child who was slowly dying of respiratory insufficiency.

One day while walking through the neonatal intensive care unit, I stopped to speak with his parents and offer whatever comfort I could. Daniel's mother and father spent hours each day at the bedside of their child and hours more at home focused on his illness and his need to recover. The picture I saw told me clearly that the death of this child was imminent and unpreventable—and that his parents were completely unprepared for this eventuality. Indeed, all of their energies were directed at supporting him and exhorting him to get well. As I spoke with them I had a strong desire to help . . . but I did not know how.

A thought occurred to me which I initially rejected as inappropriate to my role or training, but because the thought had come to me in response to a desire to help, I re-examined it. I decided to trust it and act on it. I asked Daniel's parents if they had been in communication with their baby, and they both replied that they spoke to him constantly. I then asked them if they had been listening to him, if they had been open to the possibility that he might have something he needed to tell them. They both responded that they had not considered this possibility but expressed an openness to try.

Two days later Daniel's mom told me that she had become very still and listened and had become peaceful over her child's critical status for the first time, but that she had received no specific message from Daniel. Daniel's father told me that he had received a simple but clear message from his child: "I'm O.K." He felt certain of the message and its source. He understood this to mean that his baby would recover. I asked them to continue to listen to Daniel over the next few days.

Daniel's mother received nothing specific, but his father had a second message. This time he clearly received: "There isn't much time." He was confused and upset and told me he apparently had not gotten the first message right. I asked him to consider the possibility that both communications were correct, that Daniel was letting his parents know that he was dying . . . and that he was O.K. With understandable reluctance both parents agreed to go along with this interpretation for a time to see what happened. Out of this opening they began to focus on the possibility that their child was dying and needed their permission, their acceptance of his leaving in order for him to go.

Several days later Daniel's parents were at home at about midnight, and after a deep examination of their feelings, both realized that they had been holding on to their child's survival as the only acceptable result for them. In that moment they jointly told their son that whatever he had to do, he had their full acceptance and support. Daniel died about 20 minutes later.

The gift of this experience became apparent following Daniel's death. His parents had a profound sense of peace and in every way seemed to complete their grieving for their child soon after his death. It is now seven years later. Over this period I have had many occasions to talk with this family, and on each occasion I have been impressed with the enduring gift of the conversation that occurred between us. I have also wondered who received the greatest gift from this wonderful exchange.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
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Assistant Editors

(Vincent WR: The gift of listening. West J Med 1994; 160:81)

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Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

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3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press 1966, pp 35-51 [author of book is same as author of chapter]

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Correspondence

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7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

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8. O'Connell M: A Controlled Trial of Regional Intraarterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications **(Do not include in reference list; put in text)**

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee,* September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

(Continued from Page 24)

February 4—**Chronic Fatigue Syndrome.** LDS Hospital. Fri. Contact: LDSH.

February 7-11—**Surgical Pathology.** Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 14-18—**Update in Clinical Microbiology and Immunology.** Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

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LDSH	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 20—**Law and Medicine Symposium.** Tacoma. Thurs. Contact: PCMS CME.

January 22—**Orthopedic Update.** Seattle. Sat. Contact: Children's Hospital, (206) 526-2501.

February 12-16—**WAPA Board Certification Review Course.** Seattle. Sat-Wed. Contact: Washington Academy of Physician Assistants, (206) 441-9762.

February 25—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS CME.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

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June 9-11—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

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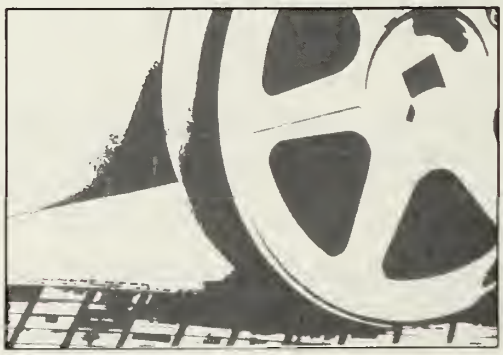

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ABSTRACTS JANUARY 1994

(Rothrock JF, Hart RG: Ticlopidine hydrochloride use and threatened stroke. West J Med 1994; 160:43-47)

Ticlopidine hydrochloride is an antiplatelet agent of proven antithrombotic efficacy that in December 1991 became available for general clinical use in the United States. The relative value of ticlopidine compared with aspirin, also an effective antiplatelet agent, has become a key clinical issue. Whereas ticlopidine is somewhat more effective than aspirin for preventing stroke in certain populations, it is also more expensive and potentially toxic. We recommend its use for patients with threatened stroke who are intolerant of aspirin and for patients who have cerebral ischemic symptoms despite aspirin therapy. Patients surviving major ischemic stroke make up a third group for whom ticlopidine use may be recommended in preference to aspirin. The use of ticlopidine rather than aspirin in patients with other cerebrovascular conditions is not strongly supported by existing data. The risk-benefit-cost equation involving ticlopidine versus other antithrombotic therapies is complex, rendering a wide range of acceptable management practices. If reliable laboratory monitoring for neutropenia during the first 3 months of therapy is not feasible, ticlopidine should not be used.

CEREBROVASCULAR DISEASE
THROMBOEMBOLISM
ASPIRIN
ANTIPLATELET
TICLOPIDINE

(Rothrock JF, Hart RG: Ticlopidine hydrochloride use and threatened stroke. West J Med 1994; 160:43-47)

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Call: (415) 882-3376

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EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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(Continued on Page 92)

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Lawrence Livermore National Laboratory is located in the Livermore Valley, 45 minutes southeast of San Francisco. To apply, please send resume and salary history in confidence to **Patricia G. Revell**, Recruitment and Employment Division, Lawrence Livermore National Laboratory, PO Box 5510, L-725, Dept. #AJWAC13PR, Livermore, CA 94551 or fax it to (510) 422-0815. Questions may be directed to John Spickard, M.D. or Kathleen Noonan, R.N., M.P.H. at (510) 423-6903. U.S. citizenship required. We are proud to be an Equal Opportunity Employer. M/F/D/V.

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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 18-23, 1994, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 7-11, 1994, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 7-9, 1994, Ritz-Carlton Maunalani, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 28-30, 1994, Sun Valley.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1994, Holiday Inn, Great Falls.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1994, Coronado, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 5-7, 1994, Society Office, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-24, 1994, University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 22-24, 1994, Wenatchee.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 9-11, 1994, Jackson Lake Lodge, Moran.

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1. Short-term treatment of active duodenal ulcer.
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3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of active, benign gastric ulcer.
5. Treatment of gastroesophageal reflux disease (GERD).
6. Treatment of endoscopically diagnosed erosive esophagitis.

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CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug or any of the ingredients.

PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.
3. Rare reports suggest that Zantac may precipitate acute porphyric attacks in patients with acute porphyria. Zantac should therefore be avoided in patients with a history of acute porphyria.

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Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias and myalgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported.

When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

Studies in dogs receiving dosages of Zantac® in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) four times a day.

Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

June 1993
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Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.

Zantac® 150 Tablets/Zantac® 300 Tablets:
Glaxo Pharmaceuticals, Research Triangle Park, NC 27709

Zantac® Syrup:
Manufactured for Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
by Roxane Laboratories, Inc., Columbus, OH 43216

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One Of A Kind

For The Treatment Of Reflux Disease, Duodenal Ulcer Disease, And Benign Gastric Ulcer

Please see Brief Summary of Prescribing Information on adjacent page.

Glaxo/Roche

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Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

Discover The Elegance Of A Hybrid

At first glance, it's the beauty of the hybrid Lily that catches the eye. The vibrant color. The delicately shaped petals. But study it more closely, and its *elegance* becomes apparent–a gentle blend of softness and strength.

At first glance, it's the enhanced performance of Vaseretic® that catches the eye. But study Vaseretic® more closely, and its *elegance* becomes apparent. The way its one-tablet, once-a-day dosage minimizes multiple medications. Minimizes the number of insurance copayments. And minimizes potassium supplementation.

A hybrid blending of tolerability and power that's available for the right patient. Vaseretic® is indicated for the treatment of hypertension in patients for whom combination therapy is appropriate.

And an elegant discovery for your practice.

VASERETIC® 10-25 *Next*

Enalapril Maleate-Hydrochlorothiazide

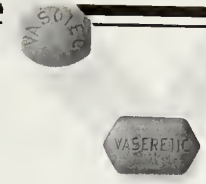
Vaseretic® is contraindicated in patients who are hypersensitive to any component of this product or to other sulfonamide–derived drugs and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Dosage must be individualized; the fixed combination is not for initial therapy. **Evaluation of the hypertensive patient should always include assessment of renal function.** For a Brief Summary of Prescribing Information, see adjacent pages.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

10 mg



25 mg

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General; Enalapril Maleate; Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions,* and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy; Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality,* below.)

Enalapril Maleate; Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalaprilat, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide; Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General; Enalapril Maleate; Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions.*)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients; Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension. Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions; Enalapril Maleate; Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium. Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide; When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs— In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution

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assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse bone marrow assay.
Enalapril Maleate: There was no evidence of a tumongenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.
Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.
There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.
Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.
Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.
Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.
Pregnancy; Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*
Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.
The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).
Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.
Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)
Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)
Cough: See PRECAUTIONS, *Cough.*
Clinical Laboratory Test Findings: Serum Electrolytes: See PRECAUTIONS.
Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)
Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.
Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.
Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.
Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.
Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.
Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.
Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*
Hydrochlorothiazide—Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

For more detailed information, consult your DuPont Pharma Representative or see Prescribing Information.

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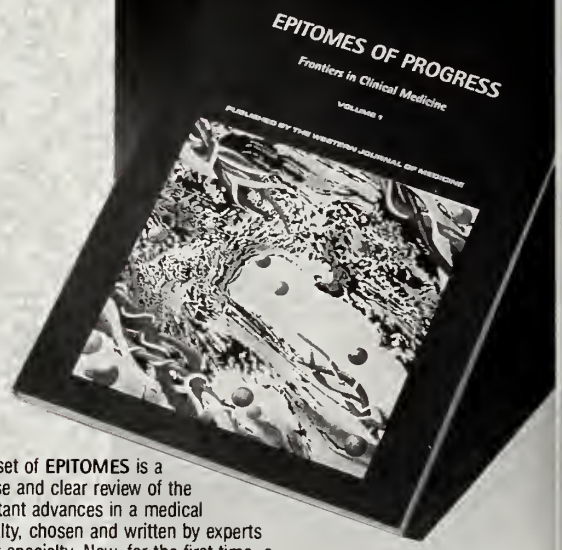
epitome

i-'pit-ə-mē\ *n* [L, fr. Gk *epitomē*, fr. *epitemnein* to cut short, fr. *epi-* + *temnein* to cut — more at TOME] (1520) **1 a :** a summary of a written work **b :** a brief presentation or statement of something **2 :** a typical or ideal example: EMBODIMENT (the British monarchy itself is the ~ of tradition —Richard Joseph) **3 :** Plural — *Epit-o-mes* — A regular FEATURE of *The Western Journal of Medicine,* now available in a single, bound volume.



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California Medical Association's Western Scientific Assembly and 123rd Annual Session

March 17-23, 1994
Disneyland Hotel, Anaheim

This FREE PROGRAM is open to all Annual Session Badge Holders

GOLDEN APPLE AWARD AND RECEPTION

"Doctor James Lind: Taking the History and Changing the History of the World"

Friday, March 18, 5:30 pm
Disneyland Hotel Convention Complex

Doctor Sherman M. Mellinkoff has been selected by the Committee on Scientific Assemblies to receive CMA's 1994 Golden Apple Award. This award spotlights exceptional physicians who have made a lifelong commitment to teaching and are renowned for their charismatic, scientific and educational talents.

Doctor Mellinkoff is Emeritus Professor of Medicine at the UCLA School of Medicine, where he served as Dean for 24 years. Following his medical education (Alpha Omega Alpha) and internship at Stanford in the mid-1940s, he served in the Army Medical Corps for two years and subsequently as Assistant, Associate and Chief Resident on the Osler Service at Johns Hopkins Hospital in Baltimore, and as Fellow in Gastroenterology at the University of Pennsylvania. In 1981 he received the Abraham Flexner Award of the Association of American Medical Colleges for his outstanding contributions to medical education.

Doctor Mellinkoff's address will explore the work of 18th century physician, James Lind, whose clinical skill changed the course of medical and world history. Between 1500 and 1800 more seamen were killed by scurvy than by all other causes. Citrus juice, Lind discovered, was a cure for scurvy, and a practical means of preventing it on long voyages. Rid of this debilitating disease, the British Navy defeated Napoleon's fleet at the Battle of Trafalgar! Correct diagnosis and treatment still rely on taking an accurate medical history. Doctor Mellinkoff will discuss the applicability of Lind's methods to modern clinical practice.

We encourage all to attend CMA's Golden Apple Award presentation and reception to help us honor this outstanding teacher.

The financial assistance of Cooperative of American Physicians, Inc. - Mutual Protection Trust is gratefully acknowledged in making this reception possible.

The Western Scientific Assembly Courses: March 17-20, 1994

CMA's 1994 Western Scientific Assembly offers an exceptional educational opportunity that meets *your needs* for clinical courses, workshops and seminars that are:

- Highest quality
- Convenient
- Practical
- Economical
- Multispecialty
- CME Approved

Primary care physicians and specialists must daily assess, evaluate, and treat patients who present with complex symptoms requiring knowledge that spans a broad range of specialties. The 1994 Western Scientific Assembly provides the most time-efficient, and cost-effective opportunity to learn the latest clinical and research developments at the largest multispecialty meeting on the West Coast!

Dozens of available courses are designed to provide you with useful, practical clinical knowledge and skills immediately applicable to your day-to-day practice needs. Courses average 3-4 hours of Category I CME credit and have also been approved for American Academy of Family Physicians prescribed credit and American College of Emergency Physicians Category I credit.

THURSDAY COURSES March 17

AM 01 Basic Cardiac Life Support

PM 02 What's Up Doc? Cartoons that Sell a Smokefree Lifestyle

03 Reducing Your Overhead and Realizing Increased Income

FRIDAY COURSES March 18

AM 04 Advanced Cardiac Life Support: Provider Course (2-day course meets Friday and Saturday)

05 Practical Neurology

06 Cost-Effective Pulmonary Medicine

07 Skin Cancer: A Clinical and Histopathologic Update

08 Pediatric Otolaryngology: What Gatekeepesr Need to Know

09 How to Improve Your Collection Results

10 GRATEFUL MED Training: Referencing the NLM Databases

PM 11 Common Neurosurgical Problems in Medical Practice

12 Emergencies in Primary Care

13 Current Issues in Dermatology

14 Cancer Detection & Follow-Up in Primary Care

15 They Can't Take That Away From Me: Medicine in Transition

SATURDAY COURSES March 19

AM 16 Advanced Cardiac Life Support: Provider Retraining

17 Pediatric Emergencies

18 Dilemmas In Women's Imaging

19 Drug & Alcohol Emergencies in Primary Care

20 New Anesthetic Agents in Ambulatory Care

21 Caring for Terminally Ill: Caring When You Can't Cure

22 Resurgence of TB: The New Face of an Old Nemesis

23 Immunologic Controversies In Private Practice

24 GRATEFUL MED Training: Referencing the NLM Databases

PM 25 Health Care Issues for Women Over 40

26 Psychiatric Emergencies in Primary Care

27 Frontiers in Nuclear Oncology

28 Practical Aspects of Occupational Medicine

29 Cultural Competence in Medical Practice

30 HIV/AIDS Essential Issues for Private Practice

SUNDAY COURSES March 20

AM 31 Urology for Primary Care Physicians

32 Multiple Views of Pain Management

33 Long Term Care Update

34 Outpatient Procedures for the Primary Care Physician

35 Future Trends in Outpatient Surgery

36 Ophthalmologist-Gatekeeper: Managed Eye Care

37 Suture Course

38 Legal Clinic on Combatting Fraud and Abuse

PM 39 Musculoskeletal Trauma in Children and Adolescents

40 Risk In Cost-Contained Care

41 No-Scalpel Vasectomy Orientation and Workshop

42 Silicone Breast Implants: Fact vs. Fiction

43 Residency Selection and Career Planning

To receive a copy of the 40-page Advance Program which provides complete objectives schedules, CME information, and registration details, please call (415) 882-3384.

This FREE PROGRAM is open to all Annual Session Badge Holders

DISTINGUISHED SPEAKER

Robert E. Rakel, MD

Sunday, March 20, 1994, 1:00 - 2:00 pm
Disneyland Hotel
Convention Complex Marina Ballroom

THE FUTURE OF GENERAL MEDICINE

Doctor Robert E. Rakel, host of "Family Practice Update" presented every Sunday on Lifetime Television, will discuss the current state of healthcare reform in the United States and the impact it will have on all physicians, especially those in primary care. Can the specialty maldistribution problem be corrected and can quality healthcare be maintained while healthcare reform focuses on lower cost? Doctor Rakel will look at the current options being proposed and offer comments on those most likely to make it through Congress.

Doctor Rakel received his MD at the University of Cincinnati, College of Medicine in 1958. Following residency training, he began his career in private practice in Newport Beach, California. Currently, Doctor Rakel serves as the Richard M. Kleberg, Sr. Professor and Chair of the Department of Family Medicine, as well as the Associate Dean for Academic And Clinical Affairs at Baylor College of Medicine in Houston, Texas. He was previously Chair of the Department of Family Medicine at the University of Iowa and the University of California, Irvine, as well as Director of the Family Practice Residency Program at Hoag Memorial Hospital in Newport Beach.

In addition, Doctor Rakel has edited several important textbooks including Textbook of Family Practice, Conn's Current Therapy, Essentials of Family Practice, and Yearbook of Family Practice. He serves on the editorial boards of Journal of the American Medical Association, The Journal of Family Practice, and Family Practice News.

We are pleased to welcome Doctor Rakel back to California this year as our Distinguished Speaker and invite all to come listen to his provocative discussion on the future of general medicine.

CMA's Western Scientific Assembly and Annual Session

CMA HOUSE OF DELEGATES

The CMA House of Delegates meets each day, Saturday, March 19 through Wednesday, March 23. House Speaker, Doctor Jack McCleary, notes that the current schedule of the House provides delegates with time to attend scientific programs, view the exhibits and participate in delegation caucuses.

Highlights of this year's House will be the farewell address of outgoing CMA President, David R. Holley, MD, a Monterey radiologist, and the inaugural address of CMA's President-Elect Ralph Ocampo, a San Diego general surgeon.

YOUNG PHYSICIANS SECTION ANNUAL ASSEMBLY

All California physicians under 40 years of age or in their first five years of practice are invited to attend the CMA Young Physicians Section (YPS) Annual Assembly which meets Friday and Saturday, March 18-19. The Assembly debates resolutions on a myriad of medical practice and health policy issues and forwards its recommendations to the CMA House of Delegates, the AMA or its own Executive Committee for action. For additional information, please contact Roger Purdy at (415) 882-5127.

CMA HOSPITAL MEDICAL STAFF SECTION ANNUAL ASSEMBLY

Medical staff leaders from throughout the state will come together at the 1994 CMA-HMSS Annual Assembly. In addition to updates on legal and legislative issues, this year's meeting will feature an educational conference on "Medical Staff Issues: 1994." For more information about the HMSS agenda, registration fees or membership, call (415) 882-5170.

EXHIBIT HALL

During the Western Scientific Assembly, the Exhibit Hall will feature exhibits for everyone: pharmaceuticals, educational displays, computer systems, office systems, insurance, investment opportunities, medical testing systems, health and home products, and much more. Admission is FREE. Be sure to alert your office managers to schedule time to visit the Exhibit Hall.

CMA ALLIANCE

Spouses of physicians can get involved at the Annual Meeting of the CMA Alliance. Board meetings are scheduled from Friday, March 18 through Sunday, March 20. The CMA-A House of Delegates meets Sunday, March 20 through Tuesday, March 22. Educational programs and a silent auction benefiting Community Health Foundation will be held on Friday and Saturday. For more information, call Patty Frisk at (415) 882-5193.

GENERAL INFORMATION

LOCATION

The CMA 1994 Western Scientific Assembly will be held at the Disneyland Hotel, 1150 West Cerritos Avenue, Anaheim, CA 92803. Call (714) 778-6600 for hotel registration information and directions.

All physicians and health professionals attending Western Scientific Assembly courses must pay general registration fees, with the exception of member medical students. Physicians and guests who do not attend any courses are not required to pay a fee. The many FREE programs include: Exhibit Hall, Golden Apple Award and Reception, a Critical Look at the Washington Scene, Distinguished Speaker, Medical Progress: A Miracle at Risk, and others.

PRE-REGISTER BY FEBRUARY 1, 1994 FOR EARLYBIRD SAVINGS

Advance registration closes February 18, after which attendees may register on site at the Disneyland Hotel's Center Lounge:

Thursday, March 17 _____ 7:00 am to 5:00 pm

Friday, March 18 _____ 7:00 am to 5:00 pm

Saturday, March 19 _____ 7:00 am to 5:00 pm

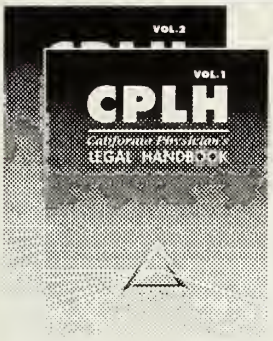
Sunday, March20 _____ 7:00 am to 5:00 pm

FOR MORE INFORMATION

Contact CMA's Western Scientific Assembly office at (415) 882-3384.

CMA Attorneys Announce the

1994 LEGAL UPDATE



The 1994 ***California Physician's Legal Handbook*** includes nearly 1400 pages designed to give you easy access and understandable explanations to the laws governing your practice.

The update includes the complete text as well as three new chapters: **Allied Health Professionals**, **Managed Care**, and **Workers' Compensation.** Written by CMA's attorneys for physicians and their advisors, this book takes the mystery out of the countless laws, regulations and court decisions applicable to California physicians.

Here's some of what you will learn about:

Abandonment / Discrimination
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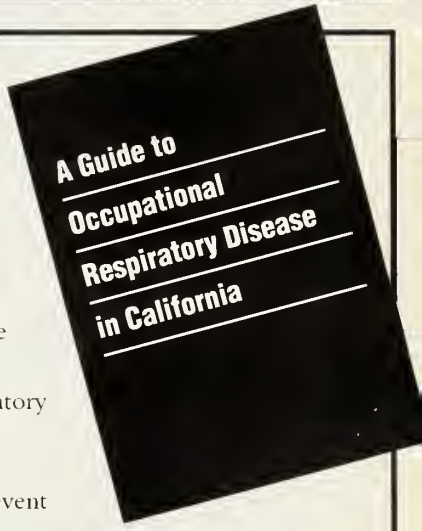
...and much more!

The all new 1994 *California Physician's Legal Handbook* contains up-to-date LAWS, REGULATIONS, COURT DECISIONS and FORMS specific to California.

FOR MORE INFORMATION CALL 415/882-5175

The California Thoracic Society, medical section of the American Lung Association of California, announces the publication of ...

A Guide to Occupational Respiratory Disease in California



Produced in cooperation with the California Medical Association, this 68-page book:

- Enhances timely diagnosis and care for patients with occupational respiratory disease
- Describes common occupational hazards to respiratory health in California
- Summarizes California requirements for medical surveillance of occupational respiratory health effects
- Describes the role of industrial hygienists in assessment and control of exposures
- Includes an extensive catalog of resources available in California to evaluate and prevent occupational respiratory disease
- Includes sample forms

Special price for
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☐ I have enclosed my check for ____ copies of *A Guide to Occupational Respiratory Disease in California*

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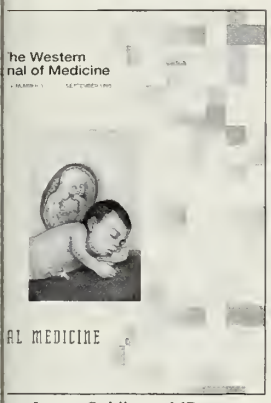

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Special Issue Editor, 1993

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- CARDIAC ULTRASOUND IN STRUCTURAL ABNORMALITIES AND ARRHYTHMIAS—RECOGNITION AND TREATMENT
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- AMNIOCENTESIS AND CHORIONIC VILLUS SAMPLING
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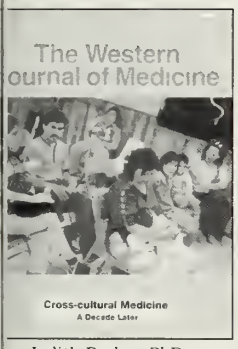

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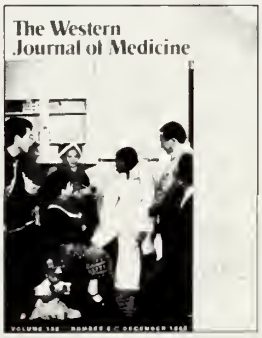

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ABSTRACTS FEBRUARY 1994

(Tong MJ, Lee SY, Hwang SJ, et al: Evidence for hepatitis C viral infection in patients with primary hepatocellular carcinoma. West J Med 1994; 160:133-138)

In testing for antibodies to the hepatitis C virus (anti-HCV) in 112 patients with primary hepatocellular carcinoma, 10 of 33 white patients (30%) and 15 of 79 Asian patients (19%) had a positive response to the antibody. The antibody profile to individual hepatitis C viral antigens and the presence of circulating hepatitis C viral RNA were determined in the 25 patients. The anti-HCV antibodies most frequently detected were toward the antigens from the core (C22) and NS3 regions. Serum hepatitis C viral RNA was present in 17 of the 25 patients (68%), and these patients tended to have serum levels of alanine and aspartate aminotransferases higher than those patients without viremia (136 ± 22 U per liter versus 64 ± 11 U per liter and 161 ± 26 U per liter versus 79 ± 14 U per liter, respectively, both $P < .05$).

Of the 15 Asian patients with hepatocellular carcinoma and anti-HCV, 4 (27%) had coexisting hepatitis B surface antigen (HBsAg) and 13 (87%) had antibodies to either hepatitis B core or surface antigen. Of the 10 white patients with anti-HCV, however, only 1 (10%) had hepatitis B virus antibodies ($P < .01$). Among 4 Asian patients with coexisting anti-HCV and HBsAg, 1 was found to have serum hepatitis B viral DNA and the other 3 had hepatitis C viral RNA. A history of blood transfusion was obtained from 12 of the 25 patients with anti-HCV (48%); 20 (80%) had coexisting cirrhosis. Our findings support the hypothesis that hepatitis C virus is an important etiologic agent in the development of primary hepatocellular carcinoma in both white and Asian patients in the United States.

PRIMARY HEPATOCELLULAR CARCINOMA **ANTI-HCV**
HEPATITIS C VIRUS

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PRIMARY HEPATOCELLULAR CARCINOMA **ANTI-HCV**
HEPATITIS C VIRUS

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ABSTRACTS FEBRUARY 1994

(Beutler E: Bone marrow transplantation beyond treatment of aplasia and neoplasia. West J Med 1994; 160:129-132)

Marrow transplantation has proved to be an important modality in the treatment of aplastic anemia, acute leukemia, and some other malignant diseases of hemopoietic cells. Much less attention has been paid to the role of marrow transplantation in the treatment of stem cell disorders such as sickle cell disease, chronic granulomatous disease, or Gaucher's disease. Allogeneic transplantation is successful in these disorders, but carries a considerable risk to the recipient. Autologous transplantation becomes a reality when efficient gene transfer with sustained expression is developed. As methods are developed to harvest hemopoietic stem cells from the peripheral blood and to amplify these cells without causing them to differentiate, transplantation will become increasingly valuable in the treatment of stem cell disorders.

BONE MARROW TRANSPLANTATION HEMOPOIETIC NEOPLASIA
HEMOPOIETIC STEM CELLS

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

February 17-20—**Seventh Annual State-of-the-Art Echocardiography.** American College of Cardiology at Tucson. Thurs-Sun. Contact: (800) 257-4739.

February 19—**Seventh Annual Epilepsy Update.** University of Arizona College of Medicine, Tucson. Sat. Contact: Lynn Mascarella, U of A.

February 21-24—**17th Annual Pediatric Update.** Phoenix Children's Hospital at Marriott's Camelback Inn Resort, Scottsdale. Mon-Thurs. Contact: (602) 239-5784.

February 24-26—**17th Annual Mid-Winter Symposium: Advances in Obstetrics and Gynecology.** American College of Obstetrics and Gynecology. American College of Obstetrics and Gynecology. Thurs-Sat. Contact: (602) 267-5366.

February 24-26—**Mayo Interactive Surgical Symposium.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Mayo Clinic-Scottsdale.

February 24-26—**Epilepsy Update: Basic Mechanisms of Anticonvulsant Treatment.** Healthspan at the Buttes Conference Resort, Phoenix. Thurs-Sat. Contact: (612) 574-7673.

June 2-4—**Arizona Medical Association Annual Meeting.** Scottsdale Plaza Resort. Thurs-Sat. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.
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ALLERGY/IMMUNOLOGY

February 18—**Environmental and Occupational Airways Disease: Clinical, Legal and Therapeutic Aspects.** Huntington Memorial Hospital at Braun Auditorium. Fri. Contact: Vivian Mishalany, Asthma and Allergy Center, (818) 397-3383.

March 19—**Immunologic Controversies Facing the Private Practitioner.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

ANESTHESIOLOGY

February 23-27—**The Practicing Physician's Approach to the Difficult Headache Patient.** Dannemiller Memorial Educational Foundation at Marriott's Rancho Las Palmas Resort and Country Club, Rancho Mirage. Wed-Sun. Contact: Seymour Diamond, 5252 N Western Ave, Chicago, IL 60625. (312) 907-6226.

March 19-20—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort. Sat-Sun. 9 hrs. $185. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

April 2-3—**22nd Obstetric/Anesthesia Conference.** Ohio State Department of Anesthesiology at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Sun. 20 hrs. $610. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

April 5-8—**Hawaiian Pain Conference.** Ohio State University Department of Anesthesiology at Grand Hyatt, Wailea, Maui. Tues-Fri. 16 hrs. $610. Contact: Arlene Rogers, Ohio State University, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8153.

April 9-10—**39th PGA Conference.** Los Angeles County Society of Anesthesiologists at UCLA Faculty Center. Sat-Sun. 13 hrs. Contact: LACSA, PO Box 90999, Long Beach 90809-0999. (213) 597-2661.

May 19-22—**California Society of Anesthesiologists Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $225-$325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

May 22-27—**Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun-Fri. 45 hrs. $500. Contact: UCSD.

CARDIOLOGY

February 25-26—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sat. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

February 26—**Cardiology for the Primary Care Physician.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

February 26-March 5—**Cardiovascular Emergencies.** UCSD at Lahaina, Maui, Hawaii. 1 week. 21 hrs. $450. Contact: Edith Bookstein, (619) 454-3212.

March 25-26—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at MGM Grand, Las Vegas, Nevada. Fri-Sat. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

April 11-13—**4th Annual Symposium on Coronary Stenting.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 13-15—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Doubletree Resort, Palm Springs. Fri-Sun. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 3-5—**Pediatric Electrophysiology, Pacing Course and Board Review.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. $425. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

July 22-24—**Coronary Heart Disease.** American College of Emergency Physicians at Marriott Tenaya, Yosemite. Fri-Sun. 11 hrs. Contact: Karen DeBont, Meetings Coordinator, 1500 W Canal Ct, Ste #500, Littleton, CO 80120-4528. (800) 421-3756.

July 24-28—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 19 hrs. Contact: UCD.

DERMATOLOGY

February 24-27—**Evaluation of Burn-Care Procedures Symposium 1994: Effects of Heparin in the Treatment of Burns.** UCSD at Marriott Hotel & Marina, San Diego. Thurs-Sun. Contact: Michael Saliba, (619) 454-9771.

March 18—**Current Issues in Dermatology.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

(Continued on Page 116)

ATTENTION ALL PHYSICIANS

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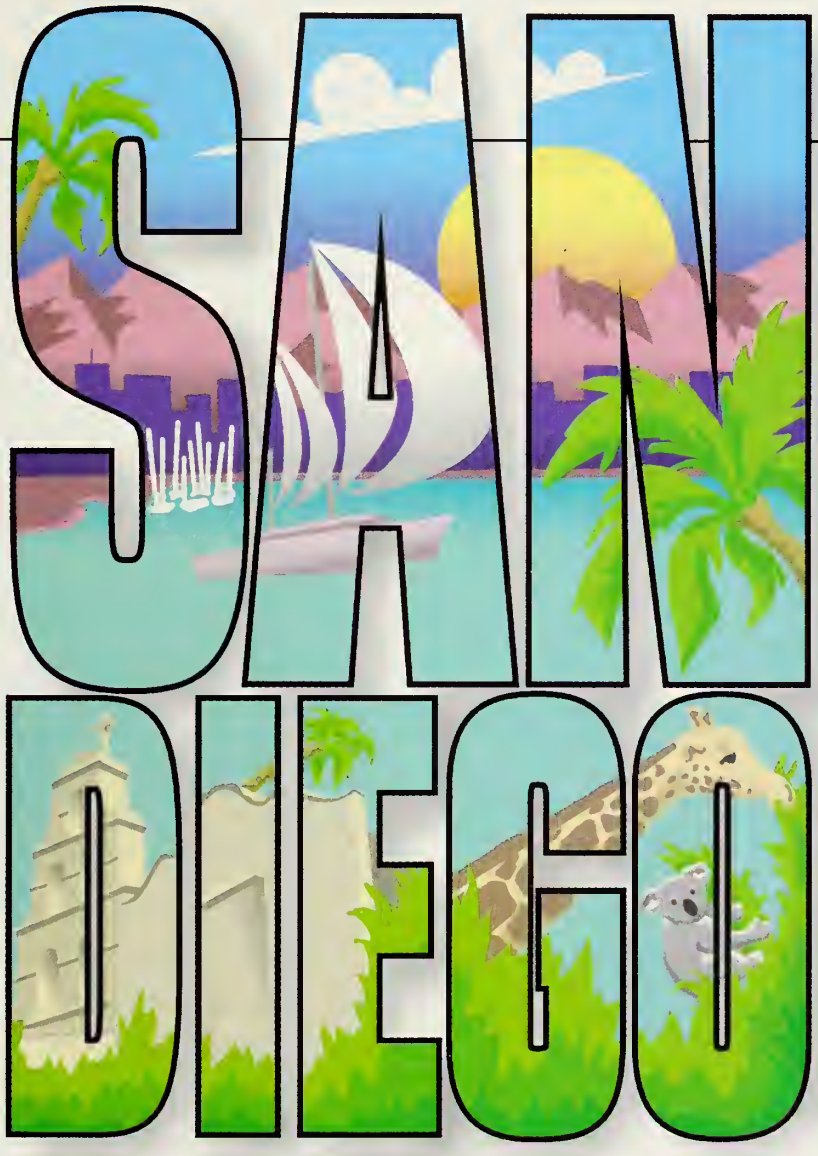

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(AANS Members will automatically receive registration information by January 31, 1994.)

The American Association of Neurological Surgeons
22 S. Washington Street, Park Ridge, IL 60068-4287

(Continued from Page 114)

July 19-23—**11th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD and Scripps Clinic at La Jolla. Tues-Sat. 33 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037 (619) 554-8556.

EMERGENCY MEDICINE

February 20-25—**Emergency Medicine 1994: 17th Annual UCD Winter Conference.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $495. Contact: UCD.

February 26-March 5—**Cardiac Emergencies.** UCSD at Royal Lahaina Resort, Maui, Hawaii. 1 wk. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 6-11—**14th Annual Mammoth Mountain Emergency Medicine Ski Conference.** American College of Emergency Physicians at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Daniel Abbott, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 14-18—**Emergency Medicine Symposium II.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

March 23-27—**Winter Wilderness Medicine: 1994.** American College of Emergency Physicians at Squaw Valley (Lake Tahoe). Wed-Sun. 21 hrs. $450. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 888-5632.

May 9-13—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 20-24—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

February 18-20—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 18-21—**46th Scientific Assembly.** California Academy of Family Physicians at Doubletree/Marriott Hotels, Monterey. Fri-Mon. 28 hrs. $235. Contact: Christine Macpherson, (415) 394-9121.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

March 4-5—**Pediatric Primary Care Conference.** California Pacific Medical Center at Eureka. Fri-Sat. Contact: Laura Johnson, (415) 923-3242.

March 18—**Cancer Detection and Follow-Up for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 19—**Emergencies in Primary Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 19—**Psychiatric Emergencies in Primary Care: A How To Primer.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20—**Outpatient Procedures for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20—**Urology for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 5.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 23-25—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $300. Contact: UCSF.

March 28-31—**Primary Care in Paradise.** Scripps Clinic and Research Foundation at Princeville Resort, Island of Kauai, Hawaii. Mon-Thurs. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

April 21-24—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

May 5-7—**Primary Care for the '90s.** University of Nevada School of Medicine at Resort at Squaw Creek, Olympic Valley. Thurs-Sat. 15.5 hrs. $260-$290. Contact: University of Nevada, Manville Bldg/342, Reno, NV 89557. (702) 784-4605.

May 11-14—**16th Semi-Annual Wound Management for Primary Care Health Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $250-$475. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

May 13-14—**Coming of Age: Geriatrics for Primary Care Providers–Part I.** UCD at Sacramento. Fri-Sat. Contact: UCD.

May 31-June 4—**21st Annual UCLA Family Practice Refresher Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Tues-Sat. 32 hrs. $485. Contact: UCLA.

June 12-17—**18th Annual Fingers to the Toes Orthopaedics for Primary Care.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. 25 hrs. Contact: UCD.

June 23-26—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 18 hrs. $370. Contact: UCLA.

July 5-7—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Tues-Thurs. 20 hrs. $350. Contact: UCSF.

1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

March 17-18—**Alzheimer's Disease Conference.** Advances in Treatment 1994. UCSD at Pan Pacific Hotel, San Diego. Thurs-Fri. 16 hrs. $195. Contact: UCSD.

March 20—**Long Term Care Update.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 30—**Caring for the Older Female Patient.** UCSF and Mount Zion Center on Aging at Miyako Hotel, San Francisco. Sat. Contact: Mount Zion Institute on Aging, (415) 750-4170.

May 13-14—**Coming of Age: Geriatrics for the Primary Care Provider—Part I.** UCD at Sacramento Inn. Fri-Sat. 13 hrs. Contact: UCD.

June 4—**Heart Disease in the Elderly.** UCSF and Mount Zion Center on Aging at Miyako Hotel, San Francisco. Sat. Contact: Mount Zion Institute on Aging, (415) 750-4170.

1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 116)

INTERNAL MEDICINE

February 17-19—**Recent Advances in Neurology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $355. Contact: UCSF.

February 19-24—**Topics and Advances in Internal Medicine.** UCSD at San Diego Marriott Hotel, San Diego. Sat-Thurs. 52 hrs. $595. Contact: UCSD.

February 26-27—**Endoscopy 1994.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce M. Fried, 10833 Le Conte Ave, Los Angeles 90024-1722. (310) 374-9708.

March 4—**20th Annual Diabetes Symposium.** UCD at Sheraton Sunrise Hotel, Sacramento. Fri. 6 hrs. $130. Contact: UCD.

March 18-20—**Current Issues in Blood Substitute Research and Development.** UCSD at Hyatt Regency San Diego on the Bay. Fri-Sun. 18 hrs. $600. Contact: UCSD.

March 18-24—**Internal Medicine: 1994.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Thurs. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 17-19—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. 12 hrs. Contact: Karen Debont. 1500 W Canal Crt, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

July 9-16—**3rd National Kaiser Permanente Internal Medicine Conference.** Permanente Medical Group at Ritz-Carlton Hotel, Kapalua, Maui, Hawaii. 1 wk. 22 hrs. Contact: Eric Tepper, MD, 3400 Delta Fair Blvd, Antioch 94509. (510) 779-5211.

OB/GYN

February 17-20—**49th Obstetrical and Gynecological Assembly of Southern California** at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB/GYN Assembly of Southern California, 5820 Wilshire Blvd, $500, Los Angeles 90036. (213) 937-5514.

March 19—**Health Care Issues for Women Over 40.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 20-24—**Pacific Coast Fertility Society Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 17 hrs. Contact: Director, Continuing Medical Education, 15731 Imperial Hwy, Ste 427, La Mirada 90638-2510. (310) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

March 5-12—**Sports Medicine.** UCSD at Wailea, Maui, Hawaii. 1 week. 21 hrs. $450. Contact: UCSD.

March 19—**Practical Aspects of Occupational Medicine.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

June 3-4—**Occupational and Environmental Medicine.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

July 25-29—**8th Annual Sports Medicine.** UCSD at San Diego Princess Resort. Mon-Fri. 20 hrs. $395. Contact: UCSD.

ONCOLOGY

February 21-23—**Clinical Hematology and Oncology: 1994.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 30—**Cancer in Women: Management of Breast and Gynecologic Malignancies.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

July 19-22—**Pan Pacific Lymphoma Conference.** University of Nebraska Medical Center at Ritz-Carlton-Mauna Lani, Kohala Coast, Hawaii. Tues-Fri. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

OPHTHALMOLOGY

March 20—**Ophthalmologist-Gatekeeper Interactions: Managed Eye Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

May 21—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

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ORTHOPEDICS

March 20—**Musculoskeletal Trauma in Children and Adolescents.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

May 19-21—**Fractures of the Shoulder and Elbow.** American Academy of Orthopaedic Surgeons at San Diego Marriott Hotel and Marina. Thurs-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

May 20-21—**New Techniques and Technologies in Total Hip Replacement.** American Academy of Orthopaedic Surgeons at Sheraton Palace Hotel, San Francisco. Fri-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

1994—**Educational Program for Musculoskeletal Evaluation and Rehabilitation.** UCSD at La Jolla. 35.5 hrs. $500. Contact: UCSD.

OTOLARYNGOLOGY

February 13-18 and March 13-18—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

March 18—**Pediatric Otolaryngology: What Gatekeepers Need to Know.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 6-8—**Temporomandibular Joint Update.** UCD at Silverado Resort, Napa. Wed-Fri. 12 hrs. $325. Contact: UCD.

PATHOLOGY

March 18—**Skin Cancer: A Clinical and Histopathologic Update.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 16—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Fri. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

May 26-28—**10th Annual Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

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PEDIATRICS

February 21-23—**Pediatrics Update 1994.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller. PO Box 84296, San Diego 92138. (619) 223-2997.

March 19—**Pediatrics Emergencies.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 15-16—**Pediatric Dermatology for the Practitioner.** Children's Hospital and Health Center at L'Auberge Del Mar Hotel, San Diego. Fri-Sat. 12 hrs. $245. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

May 12-14—**27th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

June 1-3—**13th Annual Child Abuse and Neglect Conference.** UCD at Radisson Hotel, Sacramento. Wed-Fri. Contact: UCD.

June 24-26—**Current Concepts in Child Neurology 1994.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15 hrs. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

July 15-17—**2nd Annual Pediatric Update.** Stanford University School of Medicine at Lucile Packard Children's Hospital, Palo Alto. Fri-Sun. Contact: Elinor Meyer, Medical Outreach Dept, 725 Welch Rd, Palo Alto 94304. (415) 497-8554.

PSYCHIATRY

February 18-20—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 16 hrs. $475. Contact: UCSD.

February 26—**1994 Sleep Medicine Update.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5-6—**Basic Hypnosis: A Hands-On Workshop.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 13 hrs. $295. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (310) 475-1260.

March 5, 6, 19, 20—**Introductory Workshop in Clinical Hypnosis for Physicians, Dentists and Psychologists.** San Francisco Academy of Hypnosis at Alta Bates Hospital, Berkeley. Sat-Sun. 28 hrs. $375. Contact: San Francisco Academy of Hypnosis, Verna Carter, 29 Pinto Ave, San Francisco 94132. (415) 239-4104.

March 6—**Trance Patterns and Metaphors.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sun. 6 hrs. $150. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (310) 475-1260.

April 8-9—**West Coast Neuropsychology Conference: Part I.** UCSD at Pan Pacific Hotel, San Diego. Fri-Sat. 9 hrs. $175. Contact: UCSD.

April 9-11—**West Coast Neuropsychology Conference: Part II.** UCSD at Pan Pacific Hotel, San Diego. Sat-Mon. 14 hrs. $325. Contact: UCSD.

April 22-26—**The Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Colonial Inn, La Jolla. Fri-Tues. 26 hrs. $550. Contact: UCSD.

April 30-May 1—**Self Psychological Revolution: Psychotherapy Since Kohut.** UCSD at Pan Pacific Hotel, San Diego. Sat-Sun. 13 hrs. $325. Contact: UCSD.

1994—**Basic Clinical Hypnosis Training.** UCSD at La Jolla. Ongoing. 30 hrs. $245. Contact: UCSD.

RADIOLOGY

February 14-18—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 30 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 21-25—**Contemporary Diagnostic Imaging.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, Kapalua, Hawaii. Mon-Fri. 20.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925.

March 2-4—**14th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $350. Contact: UCSF.

March 4-6—**Women's Imaging Symposium: 1994.** UCSD at Catamaran Resort Hotel, San Diego. Fri-Sun. $495. Contact: UCSD.

March 7-10—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Thurs. 30 hrs. $625. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 19—**Dilemmas in Women's Imaging.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20-25—**UCLA General Radiology Review Course.** UCLA at Doubletree Hotel, Marina Del Rey. Sun-Fri. 40 hrs. $420. Contact: UCLA.

March 21-26—**Musculoskeletal and Neuro MRI.** UCSD at La Costa Resort and Health Spa, Carlsbad. Mon-Sat. 19.5 hrs. $550. Contact: UCSD.

April 3-8—**14th Annual Residents Radiology Review Course.** UCSD at Hotel Del Coronado, San Diego. Sun-Fri. 41 hrs. $450. Contact: UCSD.

April 9—**Interventional Radiology.** UCSD at Hotel Del Coronado, San Diego. Sat. 8 hrs. $135. Contact: UCSD.

April 17-22—**Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: UCSD.

1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

1994—**Visiting Fellowship Program of Endovaginal Sonography: Focus on Techniques and Application.** UCSD Medical Center. Monthly. 30 hrs. $600. Contact: UCSD.

SURGERY

March 24-25—**9th Annual Course in Colon and Rectal Surgery.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Thurs-Fri. Contact: Donna Bowker, 1975 Zonal Ave, KAM 307, Los Angeles 90033. (213) 342-2555.

March 24-26—**6th Annual Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

June 23-25—**20th Annual Meeting of the Western Thoracic Surgical Association.** WTSA at Resort at Squaw Creek, Olympic Valley. Thurs-Sat. Contact: WTSA, (508) 526-8330.

GENERAL/MULTIDISCIPLINARY

February 14-18—**5th Annual Physician Heal Thyself.** UCSD at Palm Springs Hilton. Mon-Fri. 16 hrs. $395. Contact: UCSD.

March 18-19—**Healthcare in Transition.** California Pacific Medical Center at San Francisco. Fri-Sat. Contact: Laura Johnson, (415) 923-3242.

March 20—**Risk Issues in Cost Contained Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 25-27—**63rd Clinical Conference.** Research Study Club at Huntington Ritz-Carlton Hotel, Pasadena. Fri-Sun. 15 hrs. Contact: Louise Ball, PO Box 1216, Murrieta 92564. (909) 677-4482.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

February 19-26—**Neurology Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

(Continued on Page 122)

CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

MARCH 4-6, 1994

PHYSICAL MEDICINE & REHABILITATION
LOCATION: New Orleans, Louisiana
SPECIALTY: Physical Medicine, Physiatry, Orthopaedics
CME CREDIT: AMA Category I
FEE: SMA Member $310; Nonmember $435; Nonphysician $225

MARCH 10-12, 1994

SEC SPORTS MEDICINE
LOCATION: Memphis, Tennessee
SPECIALTY: Orthopaedics, Family Practice, Sports Medicine
CME CREDIT: AMA Category I
FEE: SMA Member $250; Nonmember $400; Nonphysician $125

MARCH 10-13, 1994

GASTROENTEROLOGY UPDATE
LOCATION: Howey-in-the-Hills (Orlando), Florida
SPECIALTY: Gastroenterology, Internal Medicine
CME CREDIT: AMA Category I, 15 hours
FEE: SMA Member $375; Nonmember $500

MARCH 18-20, 1994

DEPRESSION AND ANXIETY UPDATE
LOCATION: Hilton Head, SC
SPECIALTY: Primary Care, Psychiatry
CME CREDIT: AMA Category I, 15 hours
FEE: SMA Member $310; Nonmember $435

APRIL 7-10 1994

FOCUS ON THE FEMALE PATIENT
LOCATION: Howey-in-the-Hills (Orlando), Florida
SPECIALTY: Primary Care, Ob/Gyn
CME CREDIT: AMA Category I
FEE: SMA Member $310; Nonmember $435

APRIL 15-17, 1994

ADDICTION MEDICINE
LOCATION: New Orleans, Louisiana
SPECIALTY: Primary Care, Psychiatry, Emergency Medicine
CME CREDIT: AMA Category I, 15 hours
FEE: SMA Member $350; Nonmember $475

APRIL 15-17, 1994

ORTHOPAEDIC UPDATE
LOCATION: Wrightsville Beach, NC
SPECIALTY: Orthopaedic Surgery
CME CREDIT: AMA Category I, 14 hours
FEE: SOA Member $125; SMA Member $225; Nonmember $350

APRIL 22-24, 1994

INFECTIOUS DISEASES
LOCATION: Fort Lauderdale, Florida
SPECIALTY: Primary Care
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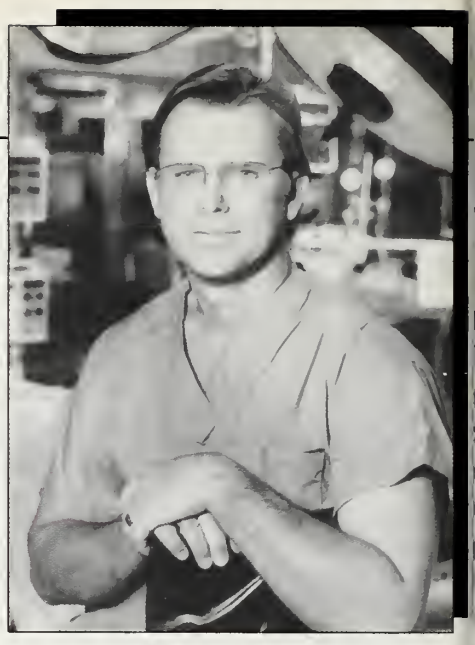

Vaughn A. Starnes, M.D. has joined the University of Southern California School of Medicine.

Vaughn A. Starnes, M.D., has joined the University of Southern California School of Medicine as Professor of Surgery, Chief of the Division of Cardiothoracic Surgery and Director of the USC Cardiothoracic Center at USC University Hospital, Childrens Hospital Los Angeles and Los Angeles County+USC Medical Center. Dr. Starnes is a world-recognized leader and innovator in adult and pediatric heart, heart-lung and lung transplantation and treatment of congenital heart disease.

In 1984 Dr. Starnes was accepted to the Stanford Cardiothoracic program, where he completed two years as a resident in cardiovascular surgery, and one year as chief resident in cardiac transplantation under the guidance of Norman Shumway, M.D.

In 1988 Dr. Starnes was appointed director of Stanford's heart-lung transplantation program, and later became chief of pediatric heart surgery and director of the transplant program at Stanford's Lucile Salter Packard Childrens Hospital. He performed about 400 adult and pediatric cardiac cases annually at Stanford. In addition to his adult cardiothoracic surgical expertise, Dr. Starnes earned a national reputation for his work in pediatrics.

Dr. Starnes also pioneered lung and heart-lung transplant procedures in children that previously had only been performed on adults. In 1991 he was the first surgeon to transplant the left upper lobe of a 2-year-old donor into a newborn with pulmonary hypertension who could not be weaned off ECMO (Extracorporeal Membrane Oxygenation). In 1992, he performed the first lung transplant on a baby with congenital diaphragmatic hernia.

USC Cardiothoracic Center

New Era of Excellence

The arrival of Vaughn A. Starnes, M.D., at the University of Southern California School of Medicine marks a new era of excellence in the treatment of cardiovascular disease. This commitment is exemplified in the creation of the USC Cardiothoracic Center at USC University Hospital, Childrens Hospital Los Angeles and Los Angeles County+USC Medical Center.

Comprehensive Services

The USC Cardiothoracic Center is one of a handful of centers in the country to provide a comprehensive range of adult and pediatric cardiovascular services including adult and pediatric heart, heart-lung and lung transplantation.

The Center features a non-invasive vascular diagnostic laboratory, diagnostic angiography laboratory and state-of-the-art cardiac catheterization laboratories. If indicated, cardiac surgeons incorporate the latest corrective surgical techniques for conditions such as ventricular and atrial arrhythmias and aortic diseases that involve aneurysms and dissections.

The Center also specializes in the treatment of infants with congenital heart defects including hypoplastic left heart syndrome, aortic valve disease, and transposition of the great vessels.

Collaboration of Specialists

At the Center, cardiologists, cardiothoracic surgeons, vascular surgeons, anesthesiologists, radiologists, interventional radiologists and allied medical professionals pool their extensive knowledge and expertise to provide patients with the full range of diagnostic and treatment alternatives.

Goal-Directed Research

As a university-based program, the Center is actively engaged in research. Specialists identify clinical problems and then seek the answer in the laboratory. Patients benefit from this link between bench and bedside, which promises to provide a better understanding of the physiology of the disease process.

Community Resource

As a vital component of the USC School of Medicine, the USC Cardiothoracic Center serves as a key educational resource for community-based and referring physicians. Physicians are encouraged to contact the Center through PACE to obtain telephone consultations, and access information regarding new patient care techniques, medications and research protocols to receive assistance with patient management concerns.

A new era is unfolding at the USC School of Medicine. We invite you to be a part of it. For more information about the USC Cardiothoracic Center, or to refer a patient, dial:
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(Continued from Page 118)

February 19-26—**Obstetrics and Gynecology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 3—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Sat-Thurs. Contact: U of Colo.

February 26-March 4—**Crash '94 Colorado Review of Anesthesia.** University of Colorado School of Medicine at Radisson Resort, Vail. Sat-Fri. Contact: U of Colo.

February 26-March 5—**Pediatrics Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 5—**Infectious Disease Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Primary Care Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Minding the Body/Mending the Mind.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 6-11—**14th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Continuing Education Center, (402) 559-4152.

March 12-19—**Sports Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 12-19—**Urology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 19-26—**Cancer Treatment Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 20-23—**Colorado Conference on Decision-Based Family Practice.** University of Colorado Health Sciences Center, Denver. Sun-Wed. Contact: U of Colo.

June 12-18—**40th Annual Family Practice Review.** University of Colorado Health Sciences Center at YMCA of the Rockies, Estes Park. Sun-Sat. Contact: U of Colo.

August 15-20—**Breast Imaging and Intervention Into the 21st Century.** Radiology Imaging Associates at Broadmoor Hotel, Colorado Springs. Sun-Fri. Contact: Ryals & Associates, (404) 641-9773.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

Every Friday (except 4th Friday of month)—**Various Topics in Contemporary Medicine (Midday CME Series).** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

February 18-20—**Ada County Medical Society—35th Annual Medical Winter Clinics—An Anthology of Clinically Relevant Topics for All Physicians.** Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. $125, Idaho Medical Society members; $175, nonmembers. Contact: Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930 or (208) 386-2135.

May 5-7—**Idaho Academy of Family Physicians 46th Annual Meeting.** Coeur d'Alene Resort, Coeur d'Alene. Thurs-Sat. Contact: Irma Sparks, Executive Director, Idaho Academy of Family Physicians, 777 N Raymond, Ste 100, Boise 83704. (208) 323-1156.

July 28-30—**Idaho Medical Association—Annual Meeting.** Sun Valley. Wed-Fri. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 25-26—**Twenty-Second Annual New Mexico Thoracic Society Lung Disease Symposium.** Santa Fe. Fri-Sat. Contact: Billie Dytzel, (505) 265-0732.

March 12-13—**Pediatric Rheumatology and Asthma—The Wylder Lectures, 1994.** Savage Auditorium, Presbyterian Hospital, Albuquerque. Contact: Steve Yabek, MD, (505) 848-3700.

May 6-7—**New Mexico Medical Society Annual Meeting.** The Marshall Building, Albuquerque. Fri-Sat. Contact: Elsa Hall, 7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237.

July 18-22—**Imaging 1994.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

February 17-19—**UOS Annual Winter Ski Meeting.** Yarrow Hotel, Park City. Thurs-Sat. Contact: UOS.

February 17-24—**37th Anesthesiology Update: Anesthesia and the Nervous System.** Snowbird Cliff Lodge. 1 week. Contact: UUSM.

February 23-26—**Ninth Annual Pediatric Emergency Medicine Conference.** Park City. Wed-Sat. Contact: PCMC.

February 23-27—**Physical Medicine and Rehabilitation Update.** Prospector Square Conference Center, Park City. Wed-Sun. Contact: UUSM.

February 27-March 2—**35th Annual OB/GYN Update.** Yarrow Hotel, Park City. Sun-Wed. Contact: UUSM.

March 2-5—**Surgical Oncology Update.** Yarrow Hotel, Park City. Wed-Sat. Contact: UUSM.

March 6-11—**Advances in Internal Medicine.** Cottonwood Center, Snowbird. Sun-Fri. Contact: UUSM.

March 8-12—**Microsurgery Workshop.** University Park Hotel, Salt Lake City. Thurs-Sat. Contact: UUSM.

(Continued on Page 123)

(Continued from Page 122)

March 11-12—**Western Intermountain Neurological.** University Park Hotel, Salt Lake City. Fri-Sat. Contact: UUSM.

May 18-20—**Odgen Surgical-Medical Annual Meeting.** Ogden Park Hotel, Ogden. Wed-Fri. 21 hrs. Contact: KayLynne, (801) 625-3122.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

February 25—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS CME.

February 25-26—**The Six Essentials of Managed Care.** Seattle. Fri-Sat. Contact: Group Health Cooperative of Puget Sound, (206) 448-2499.

March 4-5—**Current Issues in Internal Medicine.** Spokane. Fri-Sat. Contact: Spokane Society of Internal Medicine, (509) 448-2513.

March 10-11—**Internal Medicine Review 1994.** Tacoma. Thurs-Fri. Contact: PCMS CME.

March 25—**Arthrogryposis and Osteogenesis Imperfecta.** Seattle. Fri. Contact: Children's, (206) 526-2501.

April 14-16—**Children's ID Conference.** Seattle. Thurs-Sat. Contact: Children's, (206) 526-2501.

April 22-23—**Surgical Update 1994.** Tacoma. Fri-Sat. Contact: PCMS CME.

April 29—**Nuts, Bolts, and Innovation in Gastrointestinal Disease II.** Tacoma. Fri. Contact: PCMS CME.

May 20—**Clinical Guidelines.** Tacoma. Fri. Contact: PCMS CME.

June 27-28—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS CME.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 9-11—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

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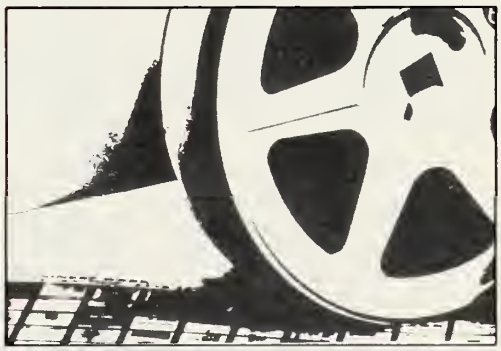

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In Memoriam

California Medical Association

Ball, Harold C., San Francisco. Died Oct 20, 1993, aged 69. Graduate of Indiana University School of Medicine, Indianapolis, 1947. Licensed in California in 1951. Dr Ball was a member of the San Francisco Medical Society.

Barlow, Ian Dean, San Francisco. Died Sep 17, 1993, aged 52. Graduate of University of Utah College of Medicine, Salt Lake City, 1970. Licensed in California in 1973. Dr Barlow was a member of the San Francisco Medical Society.

Barranco, Charles John, Del Mar. Died Oct 21, 1993, aged 72. Graduate of Medical College of Wisconsin, Milwaukee, 1946. Licensed in California in 1970. Dr Barranco was a member of the San Diego County Medical Society.

Bolduan, Nils W., Santa Barbara. Died Oct 10, 1993, aged 86. Graduate of Cornell University Medical College, New York, New York, 1933. Licensed in California in 1946. Dr Bolduan was a member of the Santa Barbara County Medical Society.

Cowan, John Francis, San Francisco. Died Oct 21, 1993, aged 76. Graduate of Stanford University School of Medicine, Stanford, California, 1943. Licensed in California in 1943. Dr Cowan was a member of the San Francisco Medical Society.

Davenport, John C., Westminster. Died Sep 25, 1993, aged 65. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1959. Licensed in California in 1962. Dr Davenport was a member of the Orange County Medical Association.

Devlin, Thomas C., Santa Cruz. Died Dec 6, 1993, aged 71. Graduate of Northwestern University School of Medicine, Chicago, Illinois, 1947. Licensed in California in 1959. Dr Devlin was a member of the Santa Cruz County Medical Society.

Edwards, Martin Dale, San Francisco. Died Dec 26, 1993, aged 71. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1945. Licensed in California in 1949. Dr Edwards was a member of the San Francisco Medical Society.

Finley, Malcolm H., San Francisco. Died May 20, 1993, aged 92. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1932. Licensed in California in 1942. Dr Finley was a member of the San Francisco Medical Society.

Gold, Ralph P., Foster City. Died Dec 23, 1993, aged 77. Graduate of University of Bologna, 1938. Licensed in California in 1951. Dr Gold was a member of the San Mateo County Medical Association.

Harvey, John E., Jr, Arroyo Grande. Died Oct 24, 1993, aged 59. Graduate of University of North Carolina School of Medicine, Chapel Hill, 1960. Licensed in California in 1984. Dr Harvey was a member of the San Luis Obispo County Medical Society.

Hembrow, Frank M., South Lake Tahoe. Died Sep 24, 1993, aged 65. Graduate of Stanford University School of Medicine, Stanford, California, 1960. Licensed in California in 1961. Dr Hembrow was a member of the Sacramento-El Dorado Medical Society.

Henderson, Emmett E., San Jose. Died Dec 30, 1993, aged 85. Graduate of Stanford University School of Medicine, Stanford, California, 1935. Licensed in California in 1935. Dr Henderson was a member of the Santa Clara County Medical Association.

Knudson, Jack R., Oakland. Died Nov 28, 1993, aged 75. Graduate of Northwestern University Medical School, Chicago, Illinois, 1943. Licensed in California in 1950. Dr Knudson was a member of the Alameda-Contra Costa Medical Association.

Lewis, Wilton M., San Diego. Died Oct 24, 1993, aged 84. Graduate of Northwestern University Medical School, Chicago, Illinois, 1935. Licensed in California in 1936. Dr Lewis was a member of the San Diego County Medical Society.

Li, David H., Pleasanton. Died Nov 7, 1993, aged 55. Graduate of University of California, San Francisco, School of Medicine, 1965. Licensed in California in 1966. Dr Li was a member of the Alameda-Contra Costa Medical Association.

Liebman, Leila, Berkeley. Died Nov 26, 1993, aged 63. Graduate of Harvard Medical School, Boston, Massachusetts, 1958. Licensed in California in 1963. Dr Liebman was a member of the Alameda-Contra Costa Medical Association.

Lubin, Albert J., Woodside. Died Jul 18, 1993, aged 79. Graduate of Stanford University School of Medicine, Stanford, California, 1939. Licensed in California in 1939. Dr Lubin was a member of the San Mateo County Medical Association.

Pasnick, Lila J., Anaheim. Died Oct 10, 1993, aged 62. Graduate of University of Oregon Medical School, Portland, 1956. Licensed in California in 1959. Dr Pasnick was a member of the Orange County Medical Association.

Schneider, Jeffrey Thomas, San Francisco. Died Dec 14, 1993, aged 47. Graduate of State University of New York Downstate, Brooklyn, 1971. Licensed in California in 1972. Dr Schneider was a member of the San Francisco Medical Society.

Starr, William R., San Jose. Died Dec 15, 1993, aged 78. Graduate of Chicago Medical School, Chicago, Illinois, 1946. Licensed in California in 1954. Dr Starr was a member of the Santa Clara County Medical Association.

Tieche, Henry L., Fresno. Died Nov 6, 1993, aged 87. Graduate of University of Michigan Medical School, Ann Arbor, 1945. Licensed in California in 1950. Dr Tieche was a member of the Fresno-Madera Medical Society.

Weber, Jaroy, Palo Alto. Died Dec 18, 1993, aged 53. Graduate of Duke University School of Medicine, Durham, North Carolina, 1966. Licensed in California in 1967. Dr Weber was a member of the San Mateo County Medical Association.

Williams, Donald C., Sunnyvale. Died Jun 1993, aged 58. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1960. Licensed in California in 1961. Dr Williams was a member of the Santa Clara County Medical Association.

Yates, Charles D., San Francisco. Died Aug 31, 1993, aged 60. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1964. Licensed in California in 1966. Dr Yates was a member of the San Francisco Medical Society.

New Mexico Medical Society

Kermott, Cameron, Farmington. Died Nov 1, 1993, aged 45. Graduate of University of Guadalajara, Mexico, 1978. Licensed in New Mexico in 1985. Dr Kermott was a member of the San Juan County Medical Society.

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Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus, E. coli*, and *Klebsiella* spp

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli, Klebsiella* spp and *Enterobacter* spp

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate

Contraindications: A history of allergic reactions to any penicillin is a contraindication

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is 1 primary cause of "antibiotic associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who received ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently

Augmentin should not be co-administered with Antabuse® (disulfiram)

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%)

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache

The following adverse reactions have been reported for ampicillin class antibiotics

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS)

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely

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When you suspect ß-lactamase-resistant otitis media and sinusitis*

The bugs stop here

AUGMENTIN®

amoxicillin/clavulanate potassium

Augmentin®: 8 years of undiminished efficacy[1]

- Clinical response rates of 96% in otitis media[2] to >99% in sinusitis[3]
- Latest† *in vitro* susceptibility‡: still impressive – *H. influenzae*: 100% and *M. catarrhalis*: 99.8%[4]
- Actively destroys ß-lactamase[5,6]

* For susceptible strains of indicated organisms. *Augmentin* is appropriate initial therapy when you suspect ß-lactamase-producing organisms.

† Latest available annual data: January to December 1991.

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

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Articles

Bone Marrow Transplantation Beyond Treatment of Aplasia and Neoplasia

ERNEST BEUTLER, MD, *La Jolla, California*

Based on a paper presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 17-18, 1993.

Marrow transplantation has proved to be an important modality in the treatment of aplastic anemia, acute leukemia, and some other malignant diseases of hemopoietic cells. Much less attention has been paid to the role of marrow transplantation in the treatment of stem cell disorders such as sickle cell disease, chronic granulomatous disease, or Gaucher's disease. Allogeneic transplantation is successful in these disorders, but carries a considerable risk to the recipient. Autologous transplantation becomes a reality when efficient gene transfer with sustained expression is developed. As methods are developed to harvest hemopoietic stem cells from the peripheral blood and to amplify these cells without causing them to differentiate, transplantation will become increasingly valuable in the treatment of stem cell disorders.

(Beutler E: Bone marrow transplantation beyond treatment of aplasia and neoplasia. West J Med 1994; 160:129-132)

The first recorded effort to transplant marrow from one human to another was when Osgood and co-workers in 1939 intravenously infused marrow cells into a patient with aplastic anemia,[1] but it was not until the 1950s that serious attempts were made to implement marrow transplantation as a therapeutic modality. By 1961 bone marrow transplantation had been used in 57 patients to treat acute leukemia.[2] None enjoyed a long remission, and most died within the first month or so of transplantation. Tissue typing had not been developed, and antibiotic and transfusion support was insufficiently advanced to bring many patients through the aplastic phase caused by the preparation for transplantation by total body irradiation.

Successful efforts to transplant marrow had to await understanding of the human leukocyte antigen system and the development of means of supporting patients who had few circulating leukocytes or platelets. In the succeeding decade, however, many advances were made, both in the understanding of transplantation immunology and in the quality of supportive care. By 1974 Thomas and colleagues had transplanted bone marrow to 37 patients with severe aplastic anemia. Although standard therapy offered these patients scarcely any chance of recovery, 17 (nearly 50%) became long-term survivors.[3]

In 1977 Thomas and associates of Seattle, Washington, reported the remarkable response of patients with acute leukemia to allogeneic bone marrow transplantation. Some patients who had far-advanced relapsed acute leukemia survived for long periods of time. The responses were best in those who were in fairly good condition at the time of transplantation. These findings were not generally appreciated at the time, but had a profound effect on my own thinking and professional activities. In the middle 1970s Karl Blume and I established a bone marrow transplantation program at the City of Hope (Duarte, California). We reasoned that if patients with far-advanced leukemia could have a good response to bone marrow transplantation, the response in patients who were in partial or complete remission at the time of transplantation should be even better. The results of marrow transplantation in this clinical setting proved to be extremely gratifying.[5,6] Thomas's group, too, had appreciated the potential of transplantation in better risk patients, and soon they published encouraging results in such patients.[7]

By 1982 several groups began to report encouraging results in the treatment of chronic myelogenous leukemia by transplantation.[8-10] Because of these successes, the vast majority of patients in the 1980s and early 1990s received bone marrow transplants for acute leukemia, chronic granulocytic leukemia, lymphomas, or aplastic anemias (Figure 1).[11] Only a few patients with genetic or metabolic disorders have received transplants, however. I will discuss what I consider to be the potential for helping these patients by bone marrow transplantation. I will also com-

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ABBREVIATIONS USED IN TEXT

G6PD = glucose-6-phosphate dehydrogenase
LTR = long terminal repeat

ment on some recent developments that should improve transplantation in all groups of patients.

Stem Cell Disorders

Although patients with sickle cell disease; thalassemia; hemolytic anemia due to pyruvate kinase, glucose-6-phosphate dehydrogenase (G6PD), or pyrimidine 5′-nucleotidase deficiency; chronic granulomatous disease; hereditary methemoglobinemia; severe combined immunodeficiency due to adenosine deaminase deficiency; and those with Gaucher's disease have different clinical syndromes, they have one thing in common. In all of these patients, their disease is due to a genetically determined protein abnormality in the progeny of hematopoietic stem cells.

Such stem cell disorders can produce symptoms that vary from mild to severe. Glucose-6-phosphate dehydrogenase deficiency and hereditary methemoglobinemia are usually not serious medical problems. On the other hand, there are disorders such as severe combined immunodeficiency and chronic granulomatous disease in which an enzyme defect produces a severe disease and in which the risk of bone marrow transplantation may be clinically justified.

Two approaches to the treatment of hereditary stem cell disorders are allogeneic transplantation and autologous transplantation.

Allogeneic Transplantation for Hereditary Stem Cell Diseases

Among the stem cell defects, the greatest gain in experience in allogeneic transplantation has been gained in thalassemia.[12] A large number of patients, particularly in Italy, have received transplants. The results have been heartening, with the mortality incidental to the procedure about 10%. Of interest, some patients have actually relapsed. We generally regard relapse as a phenomenon associated with leukemia, but in these patients the relapse signifies that the thalassemic marrow re-expanded, crowding out the normal marrow graft.

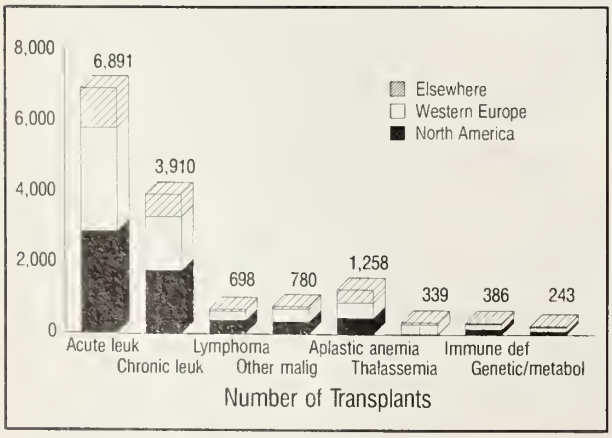

Figure 1.—Indications are shown for allogeneic or syngeneic bone marrow transplantation from a 1988-1990 survey (from Bortin et al[11]; courtesy of D. Van Epps, Baxter Healthcare Corporation). def = deficiency, leuk = leukemia, malig = malignant disease, metabol = metabolic

Transplantation has been implemented only recently in sickle cell disease.[13] Although thalassemia major is almost uniformly fatal when it is not treated, and iron chelation therapy, which may prolong life, is not available everywhere, the course of sickle cell disease is much more difficult to predict and more variable. The first transplantation in a patient with sickle cell disease was carried out in 1984, not to treat sickle cell disease, but rather to treat acute leukemia in a patient who happened also to have sickle cell disease.[14] After transplantation this patient had the sickle cell trait, having sickle and normal hemoglobin levels exactly the same as those found in the donor.

In the past few years many transplantations have been carried out for the treatment of sickle cell disease itself. In Belgium, France, and Italy, 50 patients have received transplants, and an encouraging 41 of them have survived, with a follow-up of between 1 and 75 months.[15-17] In the United States only three patients with sickle cell disease have had transplants. The follow-up is 15 to 18 months, and all three survive. There is a national collaborative protocol for transplantation in children who have suitable risk factors and an HLA-matched donor.*

What is needed in sickle cell disease is a good prognostic marker that would indicate which children should have transplants and which should not. If we knew which children would have a stroke, for example, we would know that they would need transplantation. Marrow transplantation technology has reached the stage where the mortality intrinsic to the procedure is probably less than 10%. As a result, a consensus has developed that, even lacking important prognostic information for each patient, sickle cell disease is a severe enough disorder to justify the risks of allogeneic marrow transplantation in children with a matched family donor.

Autologous Transplantation in the Treatment of Hereditary Stem Cell Diseases

The other type of transplantation, which, of course, avoids graft-versus-host disease, is autologous transplantation—harvesting marrow from a patient and then reinfusing it. Obviously this would not cure genetic diseases if the defect in the reinfused cells were not corrected. As a means to correct the genetic defect, various vectors have been used to insert genes into hematopoietic cells.

The vectors most commonly used are retroviral. Retroviruses are RNA viruses. Their RNA is reverse transcribed into DNA in the infected cell and is inserted in the

*These data were not all published at the time of this presentation, and I am indebted to Keith Sullivan, MD, University of Washington, Seattle, for providing them.

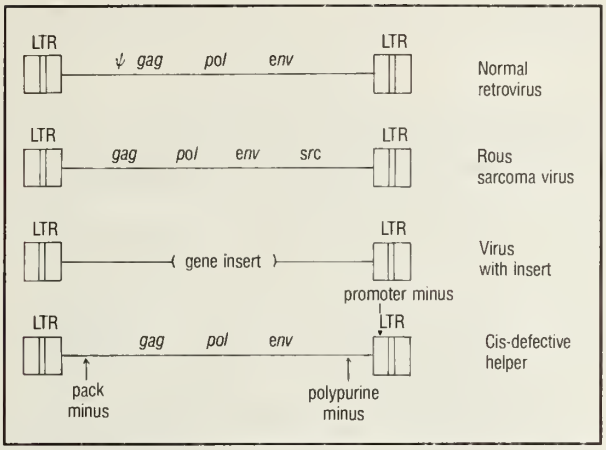

Figure 2.—The diagram shows the anatomy of retroviruses. LTR = long terminal repeat

genome and functions there in a stable manner. The prototype retrovirus is shown at the top of Figure 2. It has a relatively simple structure consisting of two end pieces designated long terminal repeats (LTRs) and three genes—*gag*, a viral glycoprotein, *pol*, the reverse transcriptase or polymerase, and *env* or the envelope gene. Some retroviruses, such as the Rous sarcoma virus, carry oncogenes.

To use retroviruses to transfer genes, the three viral genes are removed from a DNA copy of the gene and are replaced with the gene of interest, sometimes together with a selectable marker like the *neo* gene. Obviously a virus constructed in this manner could not replicate because it possesses none of the genes required for making the envelope, the reverse transcriptase, or the viral proteins. To replicate, such a vector needs a helper virus. The native virus can serve as such a helper. If it were present in the cell, it would produce the gene products that package the RNA of interest into an infectious particle. The problem is that it would also package itself, resulting in continuing infection with a retrovirus. To circumvent this problem, a defective helper, one that has several lesions that prevent it from replicating, is used. For example, a packaging region is required to package the RNA into the virus. If this region is defective in a strand of RNA, it will not be incorporated into a viral particle. The procedure, then, is to transfect a producer line with two viral constructs. One, the helper, has all of the viral genes, making possible the packaging of the gene of interest. The other contains the gene of interest, such as glucocerebrosidase for Gaucher's disease, adenosine deaminase for immunodeficiency, or any of the other genes that one might want to transfer. The virions containing the RNA version of the gene of interest bud from the producer lines and can then be used to infect the target cell. Several years ago Joseph Sorge, MD, in our laboratory used this method to transduce cell cultures from patients with Gaucher's disease. When mutant fibroblasts or lymphoblasts were infected with a retrovirus without the gene of interest, their enzyme activity did not increase. When the cells were infected with a virus that contained glucocerebrosidase complementary DNA, enzyme activity became entirely normal.[18] These cells will grow, replicate, and continue to produce the enzyme.

Lymphoblasts have been transduced fairly successfully in the treatment of children with adenosine deaminase deficiency,[19] but for most stem cell disorders lymphocytes or fibroblasts are not the target cells, but rather hematopoietic stem cells. It is much more difficult to achieve production of an enzyme in a hematopoietic stem cell and its progeny.[18] Marrow can be harvested from a mouse, the cells infected with the retroviral vector, and these cells transplanted into irradiated mice. The mice can then be killed at intervals, and one can then determine whether the gene is present and whether it is active. Serial passage can be done to determine whether a true stem cell has been transduced. Several groups have shown that in mice, the glucocerebrosidase gene does function in their macrophages.[20,21] Kohn and co-workers were able to restore the glucocerebrosidase activity to normal in marrow taken from a patient with Gaucher's disease.[22]

Serious problems attend retroviral transfer, however. First, to be effective in the treatment of most stem cell disorders, the efficiency of transduction must be high. In a disease like Gaucher's disease, thalassemia, or sickle cell disease, it is probably insufficient to correct the defect in a few cells. The defect must be corrected in most or all of the cells. Even if those cells that have been transduced are selected, it is not safe to select just 10% or 20% of the cells and administer those; a large number of stem cells is required for successful transplantation. Until recently most vectors did not provide highly efficient transduction. Second, the LTR, the promoter of retroviruses, does not provide tissue-specific regulation, which is required for some genes. For example, if hemoglobin genes are transferred into hematopoietic stem cells, they should be expressed only in erythrocytes, not in granulocytes or lymphocytes. This problem can be circumvented. In the case of hemoglobin, the locus control region seems to provide specificity for the hemoglobin gene.[23] This problem needs to be addressed in most cases of gene transfer.

The continued expression of transduced genes is a major problem when retroviruses serve as vectors. This difficulty seems to have been overcome in mice, but in primates it is more of an obstacle. Primitive cells seem to have evolved a mechanism that defends them against retroviruses by inactivating them.[24] If a viral gene does not continue to be expressed for many months and years, then the long-term aims of the procedure have not been fulfilled.

Finally, there is the lingering risk of malignant transformation. This risk is the consequence of the fact that a retrovirus is inserted into a genome in random locations. If insertion happens to be next to a regulatory gene, it may result in uninhibited proliferation of that cell. When monkeys were infected with a virus preparation that was not helper-free, lymphomas developed.[25] The risk of such transformation is minimized by using vectors that are helper-free—that is, vectors that cannot themselves proliferate. With the use of such vectors, tumors have not been observed.

New Technologies

In transplanting marrow cells, it is our aim to transfer into a patient a self-renewing cell that is capable of differentiating into erythrocytes, leukocytes, granulocytes, monocytes, and platelets. The transplantation of a cell that has already started along this pathway will result in the eventual differentiation of the progeny of the transplanted cell into a cell without renewal potential, and the graft will ultimately fail.

In the past few years we have been aware that among the bone marrow nucleated cells, a small subset of cells express the CD34 antigen on their surface. Members of this subset apparently have many of the properties of stem cells in that they are able to differentiate into all of the different lineages. Technology has now been developed that makes it possible to select these cells on a sufficient scale to transplant them. One such method uses a magnetic bead coated with an antibody against CD34. Beads are mixed with the blood or marrow, and the CD34 cells adherent to the beads are separated magnetically and are then freed from the beads by cleaving the CD34 with chymopapain. This purifies CD34 progenitor cells and, it is hoped, stem cells. An important next step not yet fully worked out is to stimulate this cell to replicate so that one cell can be expanded to 1×10^3 or 1×10^6. It is important that the amplification process does not cause differentiation. As we better understand the complex network of cytokines that regulate both the proliferation and differentiation of hematopoietic cells, such expansion without differentiation may become possible.

Another new technology consists of the transplantation of adult marrow cells into a fetus with a hereditary disorder. This approach may be successful because the fetus is immunologically naive, and therefore graft rejection is less likely. The results of trials in sheep have been encouraging,[26] and a trial in patients with chronic granulomatous disease is being planned but has not yet been implemented.

Marrow Transplantation in the 21st Century

I envision bone marrow transplantation in the 21st century as a procedure in which we will no longer actually transplant marrow. Rather, we will isolate stem cells from the peripheral blood and amplify them. In the 21st century, we will likely no longer speak of marrow transplantation but of stem cell transplantation. In the next decade, we should see more genetic diseases that are expressed in the progenitors of hematopoietic stem cells corrected by gene transfer followed by stem cell transplantation.

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Evidence for Hepatitis C Viral Infection in Patients With Primary Hepatocellular Carcinoma

MYRON J. TONG, PhD, MD; SHING-YI LEE, PhD; SHINN-JANG HWANG, MD; RUTH L. CO, RN; *and* PAUL P. C. LAI, *Pasadena;* DAVID CHIEN, PhD; *and* GEORGE KUO, PhD, *Emeryville, California*

In testing for antibodies to the hepatitis C virus (anti-HCV) in 112 patients with primary hepatocellular carcinoma, 10 of 33 white patients (30%) and 15 of 79 Asian patients (19%) had a positive response to the antibody. The antibody profile to individual hepatitis C viral antigens and the presence of circulating hepatitis C viral RNA were determined in the 25 patients. The anti-HCV antibodies most frequently detected were toward the antigens from the core (C22) and NS3 regions. Serum hepatitis C viral RNA was present in 17 of the 25 patients (68%), and these patients tended to have serum levels of alanine and aspartate aminotransferases higher than those patients without viremia (136 ± 22 U per liter versus 64 ± 11 U per liter and 161 ± 26 U per liter versus 79 ± 14 U per liter, respectively, both $P < .05$).

Of the 15 Asian patients with hepatocellular carcinoma and anti-HCV, 4 (27%) had coexisting hepatitis B surface antigen (HBsAg) and 13 (87%) had antibodies to either hepatitis B core or surface antigen. Of the 10 white patients with anti-HCV, however, only 1 (10%) had hepatitis B virus antibodies ($P < .01$). Among 4 Asian patients with coexisting anti-HCV and HBsAg, 1 was found to have serum hepatitis B viral DNA and the other 3 had hepatitis C viral RNA. A history of blood transfusion was obtained from 12 of the 25 patients with anti-HCV (48%); 20 (80%) had coexisting cirrhosis. Our findings support the hypothesis that hepatitis C virus is an important etiologic agent in the development of primary hepatocellular carcinoma in both white and Asian patients in the United States.

(Tong MJ, Lee SY, Hwang SJ, et al: Evidence for hepatitis C viral infection in patients with primary hepatocellular carcinoma. West J Med 1994; 160:133-138)

Primary hepatocellular carcinoma is a common malignant disease in many Asian and African countries. In these areas of the world, chronic infection with the hepatitis B virus (HBV) is one of the most important factors associated with the development of this rapidly fatal cancer.[1-3] After the hepatitis C virus (HCV) was cloned and the serologic test for detecting antibodies to HCV (anti-HCV) became available, the association of chronic HCV infection and hepatocellular carcinoma was more clearly defined.[4,5] Studies have indicated that in western countries and in Japan, where HBV infection is less endemic, the seropositive rate of antibody to the C100-3 antigen of HCV in patients with primary hepatocellular carcinoma ranged from 13% to 75%.[6-11] Also, the coexistence of anti-HCV with the hepatitis B surface antigen (HBsAg) and other antibodies related to HBV infection has been reported in these patients.[2,3,8-13] The role of these two coexisting hepatitis viruses in the pathogenesis of primary hepatoma remains unclear, however.

Although it is now generally accepted that the HCV is one of the major causes of acute and chronic hepatitis, a controversy remains as to whether chronic HCV infection is associated with the progression of life-threatening liver diseases. A recent study from the United States showed that after an average 18-year follow-up, the long-term mortality after transfusion-associated non-A, non-B hepatitis was no different when compared with that of the matched controls who received transfusion but in whom hepatitis C infection did not develop.[14] In that study, 11 of 568 patients with chronic non-A, non-B hepatitis died of cirrhosis, and 1 other patient died of hepatocellular carcinoma. These findings were similar to those in 984 subjects in the control group, of whom 10 died of cirrhosis and 2 died of primary hepatocellular carcinoma. Another report from Italy on patients who contracted hepatitis C after a transfusion showed that 4 of 135 patients died of cirrhosis and 1 died of hepatocellular carcinoma after a mean follow-up of 7.5 years.[15]

Our purpose in this report is to determine the frequency of HCV antibodies in a large series of Asian and white patients with primary hepatocellular carcinoma who were referred to our liver center. In these patients, HCV infection was determined by a newly developed C25 chimeric anti-HCV immunoassay. We also tested for

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
anti-HBc = antibody to hepatitis B core antigen
anti-HBs = antibody to HBsAg
anti-HCV = antibody to HCV
AST = aspartate aminotransferase
ELISA = enzyme-linked immunosorbent assay
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HCV = hepatitis C virus
OPD = O-L-phenylenediamine 2-hydrochloride
PCR = polymerase chain reaction
SOD = superoxide dismutase
TRIS = tris(hydroxymethyl)aminomethamine

antibodies directed toward individual, expressed, recombinant HCV structural and nonstructural antigens, determined the presence of coexisting past or present HBV infection, and used sensitive polymerase chain reaction (PCR) methods to detect the frequency of HCV RNA and HBV DNA in these patients.

Patients and Methods

From 1982 to 1992, the clinical data from 112 patients with primary hepatocellular carcinoma at the Liver Center, Huntington Memorial Hospital, Pasadena, California, were reviewed. Primary hepatocellular carcinoma was diagnosed either histologically or based on typical radiologic images (ultrasonography, computed tomography, celiac angiography, or magnetic resonance imaging), along with elevated serum α-fetoprotein levels (greater than the normal value of 20 μg per liter [20 ng per ml]). Underlying cirrhosis was diagnosed either histologically or clinically by the presence of either ascites or esophageal varices. Stored serum specimens were tested for HBsAg, antibody to HBsAg (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc) by using standard radioimmunoassay tests (Ausria II, Ausab and Corab, Abbott Laboratories, North Chicago, Illinois). The presence of anti-HCV, HCV RNA, and HBV DNA was determined by techniques described as follows.

Hepatitis C Virus Antigens, Multiantigen Enzyme Immunoassay, and Chimeric C25 Protein Enzyme-Linked Immunosorbent Assay

The expression of various HCV antigens and the procedures for multiantigen enzyme immunoassay and chimeric C25 enzyme-linked immunosorbent assay (ELISA) were done according to previously described methods.[16] Briefly, the C22 (119 aa), E1 (130 aa), and NS5 (942 aa) antigens, and chimeric C25 (858 aa) antigen containing segments from C22, C33C, and C100-3 were expressed as internal antigens within the yeast *Saccharomyces cerevisiae* as C-terminal fusions with human superoxide dismutase (SOD) using the method described previously for generating the C100-3 antigen.[4,5] The C33C antigen (266 aa) was expressed as an internal SOD fusion polypeptide in *Escherichia coli* using methods described earlier for the synthesis of the 5-1-1 antigen. The E2 antigen (257 aa) was expressed as a secretory protein in *Spodoptera frugiperda* insect cells by cloning the E2 gene segment downstream of the interleukin 2 signal sequence in a derivative of the baculovirus vector, PAC373.[17,18]

Recombinant HCV antigens and denatured SOD (control) were diluted to optimal concentrations in phosphate-buffered saline (pH 7.4) and coated on Immulon 1 plates (Dynatech, Chantilly, Virginia). The ELISA assays were carried out as follows: a test specimen was diluted 40-fold in sample diluent on the plate and incubated for an hour at 37°C and then washed. O-L-Phenylenediamine dihydrochloride (OPD) and hydrogen peroxide were added for horseradish peroxidase color development. The ELISA cutoff optic density values for antigens SOD, C25, C22, E1, E2, C33C, and NS5 were 0.40 plus the optic density from the corresponding antigen-negative control. The cutoff value for the C100-3 antigen was 0.45 optic density plus its negative control values. If the SOD antigen was reactive, then that specimen was considered to be nonreactive or indeterminate.

Hepatitis C Viral RNA

We established a highly sensitive reverse transcriptase-nested PCR procedure to detect the HCV RNA of all anti-HCV-positive patients with primary hepatocellular carcinoma by using the newly cloned recombinant *Thermus thermophilus* DNA polymerase.[19] Briefly, the HCV RNA was extracted from 100 μl of plasma by a single-step acid guanidinium thiocyanate-phenol-chloroform method[20] and converted into complementary DNA with recombinant *T thermophilus* DNA polymerase. The first PCR was subsequently amplified with the same enzyme.

The downstream primer of complementary DNA synthesis was mncr #2: 5′ CAT GGT GCT CGG TCT ACG AGA CCT CCC 3′ (antisense), and the upstream primer of the first PCR was L3: 5′ GTC TAG CCA TGG CGT TAG TAT-3′ (sense). The primer of the second PCR was mncr #4: 5′ CGC AAG CAC CCT ATC AGG CAG T-3′ (antisense). These primers were deduced from the highly conserved 5′ noncoding region of the HCV genome.[21,22] The primers were synthesized by using solid-phase phosphoramidite chemistry with an automated DAN Synthesizer (Applied Biosystems, models 380B, Foster City, California) and purified by reverse-phase chromatography (Poly-pak Cartridge, Glen Research Corporation, Sterling, Virginia).*

Two microliters of extracted sample RNA was added to 8 μl of a master mixture containing 1 × reverse transcriptase buffer (10 mmol per liter of tris[hydroxymethyl]aminomethamine [TRIS] hydrochloride, pH 8.3, and 90 mmol per liter of potassium chloride), 1 mmol per liter of manganese chloride, 200 μmol per liter of each diethylnitrophenyl thiophosphate, 0.75 μmol per liter of downstream primer mncr #2, and 2.5 U of rTth DNA polymerase (Perkin-Elmer Cetus, Norwalk, Connecticut). One cycle of 72°C was run for 15 minutes in a thermal cycler (Geneamp PCR system 9600, Perkin-Elmer Cetus). The mixture was kept on ice, and 40 μl of chelating

*Burt Goodman of the Amgen DNA technology group, Boulder, Colorado, assisted us in synthesizing the PCR primers.

buffer (5% glycerol, 10 mmol per liter of TRIS hydrochloride, pH 8.3, 100 mmol per liter of potassium chloride, 0.75 mmol per liter of edetate, 0.05% Tween 20) containing 1.5 mmol per liter of magnesium chloride and 0.15 μmol per liter of upstream primer L3 was added to each reaction mixture. After the initial denaturation step for 3 minutes at 94°C, 35 cycles of denaturation were carried out at 94°C for 15 seconds, and the mixture was annealed at 65°C for 15 seconds and amplified at 72°C for 15 seconds. A seven-minute longer extension step was performed after the last cycle to ensure complete polymerization. For the second round of PCR, 5 μl of the first PCR product was aliquoted to a 45-μl mixture containing 1 × PCR buffer (50 mmol per liter of potassium chloride, 10 mmol per liter of TRIS-hydrochloride, pH 8.3, 1.5 mmol per liter of magnesium chloride, and 0.01% of gelatin), 200 μmol per liter of each diethylnitrophenyl thiophosphate, 1.25 U of Taq DNA polymerase (Perkin-Elmer Cetus), and 0.2 μmol per liter of primer pairs of L3 and mner #4 and amplified similarly. After the second amplification, 10 μl of the PCR product was analyzed by electrophoresis on 1.5% agarose gel, stained with ethidium bromide, and photographed under ultraviolet light. The expected final PCR product is 233 base pairs. The following controls were carried out for each extraction and amplification step: HCV-positive control, normal control, and reagent control (without template). Throughout the whole process, the stringent contamination-control procedures were followed.[23]

Hepatitis B Viral DNA

We applied a nested-PCR procedure to amplify the HBV DNA. The primer pairs used in the procedure were from the highly conserved HBV DNA polymerase region described by Mack and Sninsky,[24] with minor modifications. These included MD03: 5′-CTC AAG CTT ATC ATC CAT ATA-3′, MD06: 5′-CTT GGA TCC TAT GGG AGT GG-3′, and SMD09: 5′-GGC CTC AGT CCG TTT CTC TTG-3′.

For HBV-DNA extraction, we used the microwave method described by Cheyrou and co-workers,[25] with minor modifications. Briefly, the microwave oven (Sharp 900 W, model R-5A83) was first allowed to warm for seven minutes at its maximum power. Thin-walled tubes (Perkin-Elmer Cetus) containing 10 μl of a patient's serum were irradiated for three minutes at 900 W. Then 45 μl of a master mixture (the same mixture used in the second HCV complementary DNA PCR amplification buffer, except that the primers were replaced by HBV primers MD03 and MD06) was added to each desiccated serum specimen. The PCR procedure was carried out by initial denaturation for three minutes at 94°C, followed by 45 cycles of denaturation at 94°C for 15 seconds, annealing at 55°C for 15 seconds, and extension at 72°C for 15 seconds. After the last cycle of amplification, a seven-minute extension was done to ensure complete polymerization. For the second round of PCR, 5 μl of the first-round PCR product was subjected to another 35 cycles of amplification under the same procedures with fresh components and a new set of HBV primers (MD03 and SMD09).

After the second PCR amplification, 10 μl of the final PCR products was analyzed by electrophoresis on a composite agarose gel made of 1.5% Nusieve and 1.5% Sea-Kem (FMC Bioproducts, Rockland, Maine), stained with ethidium bromide, and photographed under ultraviolet light. The expected size of the final PCR product was 105 base pairs.

Data in the text were expressed as a mean plus or minus the standard error of the mean. Statistical analysis was done using the Mann-Whitney U test and Fisher's exact test.

Results

Among 112 (33 white and 79 Asian) patients with primary hepatocellular carcinoma, 25 (22%) had antibodies to a chimeric C25 enzyme immunoassay test. By this assay, which contained HCV antigens C22, C33C, and C100-3, HCV antibodies were detected in 10 (30%) of 33 white and 15 (19%) of 79 Asian patients. Of the 25 patients with hepatocellular carcinoma, 13 were women and 12 were men. The mean age of the 25 patients was 58 ± 3 years (range, 29 to 76 years). All 10 white patients were born in the United States. Of the 15 Asian patients, 3 each were born in Taiwan, China, and Vietnam, 2 in Burma, and 1 each in Japan, Hong Kong, Korea, and Indonesia. A history of blood transfusion was obtained from 7 of 10 white patients (70%) and 5 of 15 Asian patients (33%) 7 to 42 years (mean 29.2 ± 3.8 years) before the diagnosis of hepatocellular carcinoma ($P = .06$). The remaining 13 patients had no history of injecting drugs, and none were health care workers. Only three patients recalled a bout of jaundice 6, 17, and 26 years before the diagnosis of carcinoma. Two patients had a substantial alcohol intake (ethanol amount greater than 80 grams per day). Of 25 patients with hepatocellular carcinoma, 20 (80%) had clinical or histologic evidence of cirrhosis. The mean serum alanine aminotransferase (ALT) level in the 25 patients was 113 ± 17 U per liter, and the mean serum aspartate aminotransferase (AST) level was 134 ± 20 U per liter. The mean α-fetoprotein level was 15,165 ± 7,796 μg per liter (range, 2.8 to 183,915).

Analysis of the antibody response of the patients to multiple HCV recombinant antigens is shown in Table 1. Of the 25 patients, 24 (96%) had antibodies to C22 and C33C recombinant proteins, 18 (72%) had antibodies to NS5, and 13 (52%) had antibodies to C100-3 and to E1. Only 4 (16%) had antibodies to E2, and none reacted to SOD.

Hepatitis C viral RNA as analyzed by PCR was present in 17 of the 25 patients (68%) (Table 1). The detection of HCV RNA in these 17 patients had no relationship to either age, sex, race, blood transfusion history, or to their anti-HCV profile. Table 2 shows the serum levels of aminotransferases in patients with and without HCV RNA. The HCV-RNA-positive patients had significantly higher serum levels of ALT and AST than those without detectable HCV viremia (136 ± 22 versus 64 ± 11 U per liter

TABLE 1.—*Race, History of Blaad Transfusion, Serum Levels of Aminotronsferose, ond Antibody Respanse to Hepatitis C Virol (HCV) Antigens and HCV RNA in 25 Patients With Primary Hepatocellular Carcinama*

		Aminotransferase, U/liter		Antibody Response to HCV Antigens							
Patients, No.	Race	Alanine*	Aspartate†	C25	C22	C33C	NS5	C100 -3	E1	E2	HCV RNA
1	White‡	367	207	+	+	+	+	–	–	–	+
2	White‡	22	55	+	+	+	+	–	+	–	–
3	White‡	59	47	+	+	+	+	+	–	–	–
4	White‡	64	63	+	+	+	–	+	–	–	–
5	White‡	63	124	+	+	+	+	+	+	+	–
6	White‡	30	55	+	–	+	–	–	–	–	–
7	White‡	83	147	+	+	+	+	+	+	–	+
8	White	63	91	+	+	+	+	–	–	–	+
9	White	67	109	+	+	+	+	+	+	–	+
10	White	56	96	+	+	+	+	+	+	–	+
11	Asian	175	317	+	+	+	+	+	+	–	+
12	Asian	57	111	+	+	–	–	–	–	–	–
13	Asian‡	52	46	+	+	+	+	+	+	–	+
14	Asian	233	480	+	+	+	+	–	–	–	+
15	Asian‡	115	135	+	+	+	+	+	+	+	–
16	Asian	119	179	+	+	+	+	–	+	–	+
17	Asian‡	143	111	+	+	+	+	+	+	+	+
18	Asian	125	174	+	+	+	+	–	–	–	+
19	Asian	103	62	+	+	+	+	–	+	–	–
20	Asian	75	97	+	+	+	–	–	+	+	+
21	Asian‡	81	71	+	+	+	+	+	–	–	+
22	Asian	273	167	+	+	+	–	–	–	–	+
23	Asian	215	150	+	+	+	–	+	+	–	+
24	Asian	171	242	+	+	+	+	+	–	–	+
25	Asian‡	19	46	+	+	+	–	–	–	–	+

+ = positive, – = negative

*Normal range, 5 to 35 U per liter. †Normal range, 10 to 40 U per liter. ‡Patients with a history of blood transfusion.

and 161 ± 26 versus 79 ± 14 U per liter, respectively, both $P = .02$). Serum ALT levels greater than 70 U per liter and AST levels greater than 80 U per liter (2 times the upper normal limit) were present in 12 (71%) and 14 (82%) of the 17 patients found to have HCV RNA, respectively, and were significantly higher than in 2 (25%) and 3 (38%) of 8 patients without HCV RNA (both $P = .04$).

Among 15 Asian patients with hepatoma, 4 (27%) had coexisting serum HBsAg antigenemia (patient numbers 11, 12, 13, and 14). Five HBsAg-negative Asian patients had anti-HBc only, and another 4 had both anti-HBs and anti-HBc (Table 3). This finding of past or present HBV infection in 13 (87%) of 15 Asian patients was significantly different from that of white patients, in whom only 1 of 10 (10%) had detectable antibodies to HBV, and this patient had anti-HBc only (patient number 8). Serum HBV DNA as determined by PCR was found in only one of the four Asian patients with coexisting HBsAg and anti-HCV (patient number 12). None of the other three HBsAg-positive patients or other patients with primary hepatocellular carcinoma with anti-HBc or anti-HBs had detectable HBV DNA.

Discussion

During a ten-year period from 1982 to 1992, 112 patients with primary hepatocellular carcinoma were referred to the Liver Center at Huntington Memorial Hospital in southern California. Our patients are multiethnic and from all socioeconomic tiers. A preliminary description of the hepatitis B and C serologic test results in Asian-American patients with hepatocellular carcinoma has been reported elsewhere.[26] Using a new chimeric C25 protein assay, we determined that 22% of our patients with hepatoma had antibodies to the HCV. If the first-generation C100-3 antigen test was used, 48% of the patients would not have been identified. Thus, the chimeric C25

TABLE 2.—*Serum Levels of Aminotransferase in Patients With Hepatitis C Viral (HCV) Antibodies to Primary Hepatocellular Carcinama and With ond Withaut HCV RNA*

	Patients		
Serum Aminotransferase Levels	HCV RNA Positive (n = 17)	HCV RNA Negative (n = 8)	P Values
Alanine, ± SEM*	136 ± 22	64 ± 11	.02†
Serum level > 70 U/liter, No. (%)	12 (71)	2 (25)	.04‡
Aspartate, ± SEM§	161 ± 26	79 ± 14	.02†
Serum level > 80 U/liter, No. (%)	14 (82)	3 (38)	.04‡

*Normal range, 5 to 35 U per liter. †Mann-Whitney U test. ‡Fisher's exact test. §Normal range, 10 to 40 U per liter.

TABLE 3.—*Hepatitis B Viral (HBV) Markers in 25 Patients With Primary Hepatocellular Carcinoma Having the Antibody to Hepatitis C Virus*

Patients	Positive for HBsAg	Positive for Anti-HBc Only	No HBV Markers
White (n = 10), No	0*	1*	9*
Asian American (n = 15), No ...	4†	9‡	2

anti-HBc = antibody to hepatitis core antigen, HBsAg = hepatitis B surface antigen

*$P < .01$ compared with Asian patients.
†Only 1 patient had HBV DNA.
‡None of the patients had HBV DNA; 4 had antibodies to HBsAg.

was highly sensitive for detecting HCV antibodies in our hepatoma patients when compared with the C100-3 assay alone.

Of our white patients, 30% had the anti-HCV antibody. A history of transfusion was obtained from 7 of the 10 white patients with hepatocellular carcinoma (70%). The mean time of the transfusion in these patients was 29 years before the diagnosis of carcinoma. Whether the length of time between transfusion and the development of cancer or this mode of transmission of HCV plays a role in the progression to cancer in patients chronically infected with HCV remains to be elucidated. A recent report from the United States on the follow-up of patients with posttransfusion non-A, non-B hepatitis showed that the few patients who died of cirrhosis and primary hepatocellular carcinoma were similar to a transfused control group in whom hepatitis did not develop.[14] Of note, the follow-up time in the former report was an average of 18 years, and additional time may be required for the development of carcinoma in these patients with chronic HCV infection.

Only 20% of our Asian-American patients with carcinoma had the anti-HCV antibody. With the exception of Japan, most Asian countries have a high HBV carrier rate, and the cases of hepatocellular cancer from these countries are mostly related to HBV infection.[2,3] In our anti-HCV-positive Asian patients with carcinoma, four also had HBsAg and nine others had antibodies to HBV. Coinfection of HBV and HCV in these patients has been reported in other countries,[8-13] and several case-control studies have suggested a synergistic effect of these two hepatitis viruses in the pathogenesis of primary hepatocellular carcinoma.[27-29] Whether past or present HBV infection coexisting with chronic HCV infection increases the risk for the development of carcinoma requires more investigation. In our four Asian patients with coexisting anti-HCV and HBsAg, one was positive for HBV DNA and the other three were positive for HCV RNA. The coexistence of HBV DNA and HCV RNA was not detected in the same patient, suggesting viral interference. This finding is consistent with that of other studies indicating that HCV may predominate over HBV in patients with chronic hepatitis coinfected with both viruses.[30-33] Only five of our anti-HCV-positive Asian patients with hepatocellular carcinoma gave a history of transfusion. The rest reported no risk factors. But previous needle contamination from health care facilities in their native countries and acupuncture remain possible routes for HCV transmission in these persons.

In our 25 patients with hepatocellular carcinoma, the anti-HCV response to multiple HCV antigens occurred most frequently to recombinant proteins from the core (C22) and NS3 (C33C) regions of the HCV genome, followed in decreasing frequency by the response to antigens derived from the NS5, NS4 (C100-3), and E1 regions. The antibody response to the expressed proteins from the E2 regions was not as frequent as to those from other regions. This may be explained in part either by the use of linear E2 epitopes rather than conformational epitopes in our assays or by the hypervariability of the HCV sequences located in the E2 regions.[34]

Although the PCR assay for HCV RNA is highly sensitive in detecting circulating HCV, the sensitivity and specificity of PCR differed among research laboratories,[35] and the reported positivity rates of HCV RNA measured by PCR in hepatoma patients has varied.[33,36-39] One report from France showed that only 4 of 19 anti-HCV-positive patients with hepatocellular carcinoma (21%) were HCV-RNA-positive by PCR.[38] Our results showed that 17 of 25 patients with carcinoma (68%) who had the antibody to HCV had HCV RNA. This finding was consistent with recent reports on Spanish and southern African black patients with hepatocellular carcinoma.[37,39] Thus, the absence of HCV RNA in eight of our anti-HCV-positive patients may be due to either the inability of our method to detect low copy numbers of viral particles or that patients with chronic hepatitis C may have intermittent viremia. It is also possible that these patients had recovered from HCV infection and the primary hepatocellular carcinoma had another cause.

Higher levels of serum ALT and AST were noted in our patients with HCV RNA than in those without detectable HCV RNA. This finding suggests that in our hepatoma patients, HCV viremia was associated with ongoing liver damage. This is consistent with previous reports that abnormal liver function was more commonly found in anti-HCV-positive blood donors and in patients with chronic hepatitis C and HCV viremia than in those without HCV viremia.[36,40,41]

The high anti-HCV seropositivity rate in patients with hepatocellular carcinoma reported in many epidemiologic studies indicates a close relationship between chronic HCV infection and the eventual progression to cancer. The development of hepatocellular carcinoma through chronic hepatitis C and cirrhosis has been noted to occur after acute hepatitis C infection.[42] The high rate of cirrhosis in our anti-HCV-positive hepatoma patients (80%) is consistent with that in previous reports[12,43-45] and supports the earlier conjecture. Our findings indicate that the hepatitis C virus is an important cause of hepatocellular carcinoma in white and Asian patients in the United States. Accordingly, patients with chronic hepatitis C should be screened for hepatocellular carcinoma on a regular basis using serum α-fetoprotein testing and ultrasonography in the hopes of detecting this cancer early. Surgical resection of small hepatomas appears to be the most effective form

of treatment because HCV infection has been reported to recur regularly in patients receiving transplantation for chronic hepatitis C infection.[46]

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Articles

An Experience in Japanese Academic Medicine

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The Japanese health care system has been highly praised for its universal access, freedom of patient choice, maintenance of a private system, and creative funding. Japanese citizens enjoy general good health, low infant mortality, and long life expectancy. Nevertheless, aspects of Japanese medical education, both graduate and undergraduate, and the structure of academic departments differ from those seen in the United States. A sabbatical spent teaching general internal medicine in Japan provided the experience for this review of the Japanese system. I describe the structure and function of departments of medicine and observations made at daily clinical teaching exercises in hospitals throughout the country.

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A sabbatical abroad provided the opportunity to observe medicine and medical education in Japan. The Sasakawa Health Science Foundation provides a way for academic physicians to visit Japan and bring their interest and expertise to the medical care system of that country. During the last eight months of 1992, I was able to study general internal medicine in Japan and to evaluate how it is taught and practiced. Certain prominent figures in Japanese medicine believe that education and training in general internal medicine and primary care in Japan should be improved, which is the reason I was invited.

My activities were centered at the Second Tokyo National Hospital, one of many affiliates of the Keio University School of Medicine, and at St Luke's International Hospital, a private facility in Tokyo with a long tradition of providing care for both Japanese citizens and foreign visitors. Both institutions have residency programs in general internal medicine. I conducted daily teaching activities at both institutions and also taught at other medical schools and hospitals around the country. I had the opportunity to interact with many Japanese academic physicians and learned much about the current methods of teaching clinical medicine in Japan and about the challenges the academic system faces within the constraints of its health care system.

Background

Japan, a constitutional monarchy about the size of the state of Montana, has a population of about 125 million. Of these, roughly a quarter live within an hour by train from the center of Tokyo. There are 47 prefectures, similar to our states, and more than 3,000 municipalities. Slightly more than a tenth of the country's area is inhabited, the rest being mountainous. This leads to a remarkable population density.

The country's history is rich and complex. Each of the four distinct historic eras—premodern Japan, the middle ages, classical Japan, and early Japan—had its own artistic, cultural, and social characteristics. Modern Japan dates from the Meiji restoration in 1868, when the previous feudal system was discontinued and the samurai—the warrior aristocracy—were demilitarized. Meiji, the emporer who reigned during the early years of that period, oversaw many of these seminal changes. During the Meiji restoration, Japan adopted a European-style democratic government and a policy of compulsory education. At the same time, imperialist ambitions led to military conflicts in Asia and, ultimately, to involvement in World War II. Thereafter, Japan entered the period of dramatic political and social reform that has attracted worldwide attention and has led to the economic preeminence the country enjoys today. In particular, from 1960 to 1987 the economy grew dramatically; now, however, the worldwide recession has caused a noticeable plateau in economic activity.

Health Care System

Western influence increased dramatically during the Meiji restoration and resulted in broad-based social legislation, including universal health care.[1,2] Although formally enacted only in 1922, guaranteed access to care had been a de facto tradition for many years before that time, stemming from a perceived responsibility of business and government to provide care. The cost of the health care system, as expressed by a percentage of the gross national product (GNP), is estimated to be about half that in the

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency virus
GNP = gross national product
HIV = human immunodeficiency virus

United States, although absolute expenditures are increasing rapidly.

Most medicine practiced in Japan is intensely private. About 80% of hospitals and nearly all offices operated by physicians (referred to generally as clinics) are private.[3] Capital development is not restricted, but the number of beds in each region is regulated by the region; this restriction is not strictly enforced, however. All patients are free to select any physician or institution for care. Physicians are reimbursed on a fee-for-service schedule negotiated for the entire country by the Ministry of Health and Welfare.[1,2] Thus, any patient has direct access to even the most prestigious hospitals. Physicians' fees are identical nationwide for any visit or diagnostic study, whether in a rural clinic or an urban referral center. Although most hospitals are private, their operation for profit is prohibited, and the institutions exist for the benefit of the community and its members.

Many physician-run offices have their own beds, although 20 or more beds makes the unit administratively a hospital. Hospitals compete intensively for the right to provide services to patients. The number of beds per unit of population is relatively high, almost 15 per 1,000.

Physicians in Japan dispense medications in their own clinics; even physicians who are full-time employees of hospitals dispense directly from the pharmacy of the institution. This phenomenon and cultural preferences of Japanese patients have resulted in more drug consumption per capita than in the United States. In Japan about a third of the overall health expenditure goes for pharmaceutical agents; in the United States about 7% is spent for drugs.

Health Care Financing

The financing of the Japanese system has always been of great interest to western countries, particularly in the United States given the current desire in this country for universal access to health care.[3] Although patients are free to choose their provider, their financing plan is limited by their employment status. These plans may be separated into three broad groups: community health insurance, employee health insurance, and insurance for the elderly.

Community health insurance covers self-employed persons, small businesses, people who are unemployed, farmers, and the dependents of these people.[1] Also included are many elderly people living on pensions. Premiums for this type of coverage, referred to as ordinary national health insurance, are determined by patients' incomes, number of dependents, and overall assets. In this plan, the municipal government is the insurer, subsidizing about half of the cost of the premiums. Patients pay 30% of the remaining cost of inpatient and outpatient care.

Employee health insurance covers almost two thirds of the population. The persons so enrolled are employees of either the government or large corporations, and they tend to have relatively high incomes. Premiums are generally divided about equally between the employer and the employee, with the employee's portion deducted from paychecks. Many employers use a progressive, income-related schedule to determine the amount of the employee's contribution. This type of insurance may be managed by the federal government, private corporations, or one of numerous insurance societies, which are jointly administered by representatives of labor and management. In addition, employee health insurance may be provided by an independent sailors' group and by mutual aid societies for governmental employees. Under each of these many plans, the co-payment rate is 10% for the employee, 20% for dependents receiving inpatient care, and 30% for those seeking outpatient care. Some companies provide additional benefits in their plans to cover these patient and dependent co-payments, and they also may reimburse for other items not typically covered by the plan, including normal deliveries and routine history and physical examination visits.[1]

A special fund pays all heath care costs incurred by persons older than 70 years, irrespective of the plan in which they had been enrolled previously. Each plan contributes to this fund, and its size is determined by the ratio of elderly persons to the population at large. Thus, no individual plan shoulders a disproportionate amount of these costs. Patient co-payments are small in this group. The rapidly increasing number of elderly Japanese will put greater financial pressure on the plans contributing to this fund.

All three plans have a monthly ceiling on how much anyone must pay; in effect, this acts as coverage for catastrophic illness. The maximum amount payable each month is approximately $440 for most Japanese citizens and about half that for the poor. As a result, few people fail to seek care because of the possible financial consequences. Countrywide, co-payments amount to about an eighth of the total health care expenditure. The features of these three plans are summarized in Table 1.

Is the cost of medical care in Japan low compared with that in America, as might be deduced from these figures?[2,3] This is a difficult question to answer. If life expectancy and infant mortality are used as general measures of quality assessment, then the Japanese do well; the average baby boy born today has a life expectancy of over 76 years, a baby girl 82 years.[3] Infant mortality is half of that in the United States.

It could be argued that the cost of care in the United States reflects a more daunting set of problems. An example is the human immunodeficiency virus (HIV) disease. In 1990, only 200 cases of the acquired immunodeficiency syndrome (AIDS) were reported throughout Japan, although the number of cases is rising slowly.[2] In the United States during the same year, there were 180,000 cases. The Japanese diet, which is rich in fish and traditionally low in fat, may also contribute to the reduced cost of health care because of fewer fat-related health prob-

TABLE 1.—*Comparison of Benefits Provided Under Japanese Health Insurance Plans*

Insurance Plan	*Insured*	*Insurer*	*Financing*
Community-based health insurance.....	Employees of small businesses, self-employed persons, farmers, some retirees	Mainly municipalities	Premiums paid by persons covered, shared with local and national government
Employer-based health insurance.....	Employees of most businesses and national and local governments	Government, health insurance societies	Premiums based on income; employer and employee contribute equally
Elderly health insurance	All people older than 70 yr, bedridden people older than 65 yr (irrespective of previous coverage	Municipalities	Local and national government, contributions from community and employee health plans

lems. Malpractice litigation is relatively rare, perhaps due in part to the small number of lawyers in Japan. No doubt cultural and sociologic considerations play a role as well in the reluctance of Japanese patients to sue their physicians. On the other hand, at least 60% of Japanese men smoke cigarettes, and throughout the country the average intake of sodium is high. Whether related or not, a significant incidence of cerebrovascular disease is noted in Japan.

As noted earlier, the dramatic expansion of the Japanese economy tended to reduce the percentage of GNP spent on health care, even as health care expenditures have grown in absolute terms. Indeed, the actual per capita health care expenditure has increased appreciably since 1960. According to Ikegami, the best measure for comparing the two countries is the compound ratio of growth rate in health spending relative to the compound in GNP[2]; by this measure, Japan has a growth rate of 1.46 and the United States 1.80, a difference of about 20%. Although still substantial, this is considerably less than the difference when measured by comparing GNPs.

On balance, the national health care system of Japan is excellent, and its cost, although increasing, is reasonable when viewed from our perspective. This is particularly so considering that catastrophic coverage and universal access are available for all Japanese citizens.

Medical Education

While in Japan, I made teaching rounds daily for the internal medicine house staff at two hospitals, and medical students were frequently present at these sessions. I also taught medical students directly in lectures at Keio University and Tokyo University and taught briefly at schools throughout the country. Japan has about 80 medical schools, both public and private. Postgraduate training occurs in both private hospitals, which include most Japanese hospitals, and in public hospitals, which are usually considerably larger.[4] Public hospitals are preferred by patients free to choose the site of their care.

Education in medical school is combined with undergraduate work, and a six-year program leading to both baccalaureate and MD degrees is standard. The last two of the six years are spent in clinical training, but in a form dramatically different from that obtained by American students.[4] In the clinical years students attend lectures and have limited opportunities to examine and interact with patients.[5] They have little direct responsibility for the care of patients, and little if any time is spent in learning and performing diagnostic or therapeutic procedures. Professors frequently recruit bright students for programs leading to a PhD, either in postgraduate education or during medical school. These students, unlike those in medical scientist training programs in the United States, often work for many years without compensation in hopes of eventually entering an academic career.

Most students who plan to practice after graduation begin with a two-year residency. Medical graduates are not legally required to have postgraduate training, but about 80% enter a program at public or private university-affiliated hospitals or at private nonaffiliated institutions authorized by the Ministry of Health and Welfare as teaching institutions. Postgraduate medical education is therefore a critical component of the system, especially given the relatively few opportunities that undergraduate medical students have to care for patients directly. Nevertheless, this training is only recommended, not required; nothing prohibits any graduate of a Japanese medical school from entering clinical practice immediately after graduation.

Residencies vary in structure from institution to institution; Table 2 provides an outline of one such program at the Kawasaki University School of Medicine. The curriculum is principally based on internal medicine; however, this varies widely from hospital to hospital. In their first and second year of training, residents assume responsibilities in patient care not unlike those assumed by third- and fourth-year medical students in the United States. Critical studies have described and analyzed postgraduate education at university and nonuniversity hospitals in Japan and have documented inconsistent training in basic clinical skills among Japanese physicians at given levels of training.[4] There is no matching plan to determine the site of postgraduate training, and the content of residencies is not consistently evaluated and regulated. Instead, individual students apply directly to institutions and often to individual professors. As a result, many students train at the schools from which they graduate, although some universities encourage students to train elsewhere. Physicians commonly practice near or in a hospital affiliated with the school from which they graduate.

My exposure to Japanese medicine was concentrated in internal medicine. Rarely does an entire department of medicine in Japan have a single chair. Instead each medical specialty, or often a group of two or three unrelated

TABLE 2.—*Postgraduate Education Curriculum in the Department of Primary Care Internal Medicine, Kawasaki University Medical School*

	Education Curriculum											
Year of Training	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	*Jan*	*Feb*	*Mar*
Junior Resident												
PGY-1		Primary care		Internal medicine, gastroenterology		Internal medicine, neurology		Internal medicine, pulmonary		Anesthesiology		General surgery
PGY-2	General surgery	Surgery elective		Primary care		Internal medicine, cardiology		Internal medicine, elective		Emergency medicine		
Senior Resident												
PGY-3	Primary care Outpatient and inpatient care, including radiology, ultrasonography, and endoscopy											
PGY-4	Orthopedics		Dermatology		Otolaryngology				Primary care			
PGY-5		Elective			Pediatrics				Primary care			
PGY-6	Community-oriented family medicine (at model clinic)											

PGY = postgraduate year

but aggregated subspecialties, is administered separately by individual professors. Thus, teaching and training in internal medicine may take place in as many as seven or eight separate departments, rather than following the US model of one large department with central administration and many subspecialty sections. As a result, no single program director has overall responsibility for the training of residents in general internal medicine. Instead, a resident is affiliated with one of the many subspecialty departments and has loyalty, as well as responsibilities, to that particular subspecialty. The lack of core training in internal medicine has also resulted in faculties being heterogeneous; often surgeons and subspecialists are general internal medicine faculty members. Residents apply directly to these small departments. General internal medicine has little academic prestige. Scholarly activities that are commonly associated with divisions of general internal medicine in the United States are in an early stage of development in Japan. Because administrative and academic power are vested in the chairs of subspecialty departments, it has been difficult for general internal medicine as an academic division to compete for top graduates, research space, and funding. Nevertheless, there is a general impression in Japanese academic circles that the public would be better served by more broad-based core training in general internal medicine and primary care.

The Kawasaki University School of Medicine curriculum provides training in some disciplines ordinarily not part of core training in internal medicine in the United States, notably upper endoscopy and radiology. It is not uncommon for a graduate of a general internal medicine residency in Japan to have done more than 50 upper endoscopies, often with a high level of skill. Diagnostic endoscopy is widely used in Japan because of the high incidence of gastric carcinoma; the procedure is typically performed without sedation on outpatients, who leave the clinic minutes after the procedure is completed. Residents also are trained more formally in radiology than they are in the United States. They commonly take and interpret their own ultrasonograms. Despite this, there is little formal academic interaction with departments of radiology except when residents are assigned to those departments. In short, medical residents who finish three years of general internal medicine—in addition to the two years of general training at the conclusion of medical school—are usually prepared adequately for a career in primary care medicine. From my own observations, residents in the fifth year of such a program were generally fairly knowledgeable about common pathophysiologic processes, were well versed in basic diagnostic and therapeutic techniques, and had seen a wide variety of common medical illnesses.

The mix of inpatient and outpatient training in general internal medicine, a subject of intense interest in this country for the past decade, is interesting to observe in Japan. Clinic responsibilities are concurrent with ward experiences, and aside from time spent in emergency departments, there is little concentrated time in the ambulatory care setting. Universal access to care and freedom to choose an institution lead invariably to large crowds and long waiting periods for patients at the type of hospital that is likely to have a training program. At the Second Tokyo National Hospital, for instance, it is not unusual to see an overflowing waiting room hours before outpatient visits start in the morning. The implications of this tendency for teaching are evident: Service responsibility makes it nearly impossible to conduct any concentrated teaching in that setting. Faculty members work side by side with residents, both seeing patients for brief visits, so that the work can be accomplished. I attended several of these clinics but found it impossible to interact with the residents on an educational basis.

In contrast, teaching on the inpatient wards is generally similar to the American situation. Residents admit patients throughout the day and night, and a detailed discussion of one or more such patients is possible at daily conferences. Usually I discussed one or two cases daily, often but not invariably those admitted the night before and selected by faculty or chief residents for their possi-

ble interest. These conferences consisted principally of a clinical discussion of the condition under question, with an attempt to provide a basic core of information about the illness under discussion.

This session was considerably different from the standard residents' report or attending rounds conducted in this country. Bedside diagnosis was not emphasized; Japanese residents had little expertise in physical examination and preferred didactic instruction of a noninteractive nature. Although over time the Japanese residents became involved in these conferences, typically they were uncomfortable when asked even rudimentary questions. This observation has been made by many others who have worked in clinical medicine in Japan. Nevertheless, attendance at these sessions was excellent and prompt, and the residents without exception took copious notes.

Attending physicians supervised residents inconsistently in the general internal medicine training programs. Attending notes to document supervision were not required; thus, the quality of care provided varied with the experience of the admitting resident. Because of the nature of the clinic coverage, however, many patients were directly admitted by attending physicians working there. In these instances, the resident providing the day-to-day inpatient care simply accepted the instruction of the staff physician, usually without much dialogue or discussion about the basis for the approach to diagnosis and treatment.

My overriding impression was that treatment was empiric and stylized, and admitting laboratory and diagnostic studies were numerous, similar to the case in the United States. An interesting variation is the common tendency for on-call residents to do ultrasonographic studies themselves and to interpret them for presentation the following morning. Overnight call schedules in the Japanese hospitals that I visited were relatively light, with perhaps four or five nights of duty per month for programs in general internal medicine. Japanese residents, however, rarely left the hospital on any day until every plan for their patients had been executed. Cross-cover responsibility as we know it is relatively uncommon, and there are no night float systems. Thus, the principal duty of on-call physicians is to admit patients. Supervising faculty members are part of the on-call rotation and admit patients on nights when no residents are covering the general internal medicine service.

In all departments, whether subspecialty or general internal medicine, surgery, or other specialties, there is a weekly tradition in Japanese medicine that I observed at every hospital. The most senior professor, usually chair of the department in question, makes rounds to visit every patient on the service, accompanied by all residents, fellows, and often additional faculty members. Although potentially useful for educational purposes, this is mainly a social exercise; the senior professor greets the patient, who obviously is honored by the visit and has an opportunity to voice feelings about his or her condition that day. The professor often conducts a cursory examination, converses with the patient for a few seconds more, and then advances to the next bed. The audiences for these activities may be as large as 10 or 15 physicians, but physical findings are rarely pointed out and demonstrated, and no other questions are advanced by junior members of the group. These rounds may take as long as two hours and, from what I gathered, are considered important by patients. Frank conversations with residents indicated concern about the amount of time expended in contrast with what is learned, but such concerns are seldom voiced publicly. On several occasions, I was asked to conduct these rounds, and I took the opportunity to make them teaching-oriented exercises. This seemed to be popular with residents and students, although possibly not with the other faculty members. In any case, bedside medicine in Japan is generally an underdeveloped art.

Missing from the teaching activities of the Japanese general internal medicine residency is the mortality and morbidity conference. This may reflect the general absence of quality assurance activities in Japanese hospitals, which is surprising considering that Japanese industry is well known for this type of activity. There is little impetus to obtain postmortem examinations on patients and little, if any, interest in reviewing the findings of such examinations. The pathologist at one of the hospitals at which I worked was clearly surprised by my presence with a medicine faculty member inquiring about an autopsy on one of our patients. Complications, when they occur, are freely admitted by responsible or involved parties but are not reviewed systematically.

In contrast to the US system, the mortality and morbidity conference, residents' report, and ward attending rounds are used infrequently in Japanese medical education. Involvement by attending physicians is sporadic and mostly directed at topics of a practical nature, such as specific therapies. Subspecialty teaching conferences are similar in some respects to those seen in the United States but are hierarchical. The lengthy average hospital stays have one advantage: They allow repeated observations of the patient and the course of the disease, which has not been possible in the United States in recent years.

English-language journals are available in all hospital libraries, but articles are rarely discussed, at least by residents. Some conferences are referred to as journal clubs; these are meetings in which one resident is assigned simply to read through an article, or even a chapter in a textbook, while the others follow along. Critical review of the literature as is common in western training centers is thus lacking, but Japanese trainees are fastidious about using standard textbooks for study, and occasionally a senior resident will bring forth a peer review article.

Use of Pharmaceutical Agents

A wide array of drugs is prescribed for Japanese patients by residents and staff, both in clinics and on inpatient services. Private practitioners prescribe their own medications; in essence, this ancillary source of income partly explains the amount of overprescribing seen in Japan. In public hospitals, although physicians do not prescribe drugs directly, they exert substantial control over

the hospital pharmacy, and there is little discourse on the merits of including a given agent on a particular hospital formulary. Pharmaceutical company representatives are much in evidence in Japan and likely have influence in the panoply of drugs that are administered. Extensive out-of-hospital benefits accrue to physicians from relationships with these representatives. It is not unusual to have such a representative host a physician and visitors at dinner, provide tickets to sporting events, or supply other benefits. In a sense, the relationship between physicians and pharmaceutical companies in Japan is similar to that between business associates in nonmedical fields. Similar practices are widespread in the United States, but they have sparked a lively debate about what the proper relationship between physicians and pharmaceutical companies should be. The apparent conflict is evident to Japanese practitioners, but it is doubtful that the nature of the relationship will be altered anytime soon.

Another factor contributing to the widespread use of pharmaceutical agents in Japan is the discomfort Japanese patients feel with invasive therapies or invasive diagnostic studies. Japanese patients are more content to trust in bed rest and medications to bring about the healing of illness and are skeptical about surgical procedures. The number of operations performed in Japan is thought to be less than half that in the United States, and my observations bear this out. As a major exception, upper endoscopy is nearly universally applied, although as it is done, few patients regard it as especially invasive. Japanese patients also rely heavily on traditional medications, and more than 2% of the prescriptions written in the country are for *kampo* therapies, herbal remedies imported to Japan from China in the sixth century.[1] In addition to these traditional medications, practices such as acupuncture and moxibustion are much in evidence, although they are usually practiced in conjunction with more orthodox treatments. In this sense, Japanese patients take a practical approach to the cure of illness, perhaps analogous to the coexistence of Buddhist and Shinto beliefs in the spiritual life of the Japanese. Ohnuki-Tierney provides an excellent review of the anthropologic and sociologic approach of the Japanese to illness,[5] and the monograph is an essential volume for anyone hoping to understand the role of illness in Japanese society.

Miscellaneous Observations

Casual visitors to a Japanese hospital are impressed with the unwillingness of physicians to discuss a diagnosis of cancer with a patient; in the hospital where I practiced and taught, many patients died of cancer without being specifically informed of the diagnosis. Rituals after death are of interest as well. It is important spiritually for the deceased to remain physically intact because of the belief that the person will return in an afterlife. This is one reason it is difficult to find cadaveric donors for transplants in Japan; organ donation would render the donor incomplete for a subsequent life. Similarly, the concept of brain death has achieved only slight acceptance, further impeding the advancement of transplantation medicine in that country. Some physicians question whether a person could be dead and still give birth, for example.

Japanese hospitals are considerably less modern than their US counterparts, although even in older buildings diagnostic equipment, such as that used in radiology suites, is modern. There are often six patients per room. The propensity of family members to remain close to the patients[5] and, indeed, to participate actively in their bedside care makes for crowded quarters. Patients seldom complain about this, however. Similarly surprising is the neglect of universal precautions. The weekly rounds mentioned previously employ adequate hand-washing techniques only occasionally as the team goes from patient to patient. Perhaps not surprisingly, every hospital has a few patients with methicillin-resistant staphylococcal infections. The nearly complete absence of HIV disease might further attenuate any pressing concern about the usefulness of proper hand washing, although young physicians appear to see this as a problem. Although HIV disease is rare in Japan, the public is aware of the possibility of its increasing importance. Incidence figures of AIDS, although low, rose during my stay. Underreporting of HIV infection is, in my opinion, not a reason for the low reported incidence. Clearly Japanese students and residents have heard much about AIDS and test for it frequently. Nevertheless, in the eight months of my visit, I did not see a single patient who was either HIV-seropositive or affected with clinical AIDS.

Hepatitis C infection is widespread in Japan; many patients on general internal medicine services have cirrhosis or hepatocellular carcinoma as a consequence. In contrast, infection with hepatitis B is relatively unusual. Heat stroke is surprisingly common in Tokyo. There may be a genetic susceptibility of skeletal muscle to rhabdomyolysis. For example, periodic paralysis, likely due to a muscle membrane defect, frequently develops in Asian men who have thyrotoxicosis. Necrotizing lymphadenitis, a condition affecting young women and presenting with cervical lymphadenopathy, fever, and hematologic abnormalities, is commonly observed. It can be difficult to distinguish this condition clinically from lymphoma, although distinctive pathologic changes are observed on biopsy specimens. Some interesting therapies included the use of plasma exchange for liver failure, dipyridamole in cases of membranous glomerulonephritis, and an extensive use of diuretics in all types of renal failure. Other clinical observations include a relatively lower incidence of Hodgkin's disease compared with non-Hodgkin's lymphoma and the relative rarity of type I diabetes mellitus despite a widespread prevalence of type II.

In the United States the possibility of pulmonary embolism is frequently discussed concerning patients in the hospital. In Japan physicians have the impression that pulmonary emboli are relatively rare, although perhaps a bias exists in the direction of underinvestigating it for this reason. Polymyalgia rheumatica, with or without giant cell arteritis, is said to be uncommon. Far more patients than would be expected appeared to have adult Still's disease, and lupus erythematosus is also common. Hyperten-

sive cardiovascular disease is extremely common in Japan, and so is stroke. Coronary atherosclerotic heart disease is seen less frequently, although its incidence is falling in the United States as well. Syndrome X, namely small-vessel ischemic heart disease, is said to be common, and I observed at least one patient who probably had this problem. Neurologic diseases in the elderly, such as Alzheimer's and Parkinson's diseases, are frequently seen in Japan, as they are in the United States.

A few differences in the use of diagnostic studies are worthy of mention. The C-reactive protein remains widespread in Japan, and as in this country, its presence indicates the need to measure the erythrocyte sedimentation rate. Chondrocalcinosis of the rib cartilage is seen nearly universally on chest radiographs in Japan. This begins at a young age and is especially frequent in women. In some chest radiographs there was more calcification in the cartilage than in the bones. I am not aware that this is associated with any systemic disorder of calcium or vitamin D metabolism, and the condition was not commented on by Japanese physicians. Hip fractures are uncommon, despite widespread osteoporosis.

Summary

Parts of the Japanese medical care system, in particular its educational system, could profit from change. Several facts should temper any enthusiasm for sweeping reform, however. To reiterate, the average life expectancy today in Japan is 82 years for a woman, 76 years for a man; the infant mortality rate is one of the lowest in the world; and the impression of a visitor is of a population in robust good health. Any changes in the system would have to improve on what are already remarkably successful indices of health. Many factors may contribute to these impressive data, such as the homogeneity of the population, the absence of injection drug use, a salubrious diet, and a high level of economic and educational attainment.

Often overlooked is the role of Japanese physicians. Clearly the training program in general internal medicine could not be considered modern by US standards, and likewise, the facilities for patients in hospitals and clinics, although availing themselves of modern technologies, are inconsistent in terms of patient comfort. Nevertheless, the typical Japanese physician, despite these obstacles, is committed, sincere, and industrious. These physicians bring a sense of dedication and commitment to the bedsides of their patients. They have rigorous intellectual honesty and are willing to admit mistakes. Warm collegiality characterizes the relationship among physicians in different specialties, which also contributes to effective care. The Japanese population is well served both by its universal health care access and by physicians whose work habits and level of commitment are exemplary. Appropriate changes made in the delivery system and in medical education generally can only signal more good news for the health of the Japanese public.

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Conferences and Reviews

The Skin as an Immune Organ

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As a protective interface between internal organs and the environment, the skin encounters a host of toxins, pathogenic organisms, and physical stresses. To combat these attacks on the cutaneous microenvironment, the skin functions as more than a physical barrier: it is an active immune organ. Immune responses in the skin involve an armamentarium of immune-competent cells and soluble biologic response modifiers including cytokines. Traversed by a network of lymphatic and blood vessels, the dermis contains most of the lymphocytes in the skin, other migrant leukocytes, mast cells, and tissue macrophages. Although the epidermis has no direct access to the blood or lymphatic circulation, it is equipped with immune-competent cells: Langerhans cells, the macrophage-like antigen-presenting cells of the epidermis; keratinocytes, epithelial cells with immune properties; dendritic epidermal T lymphocytes, resident cells that may serve as a primitive T-cell immune surveillance system; epidermotropic lymphocytes, migrants from vessels in the dermis; and melanocytes, epidermal pigment cells with immune properties. Although the components of the epidermis and dermis work in concert to execute immune responses in the skin, for purposes of this review, we focus on the cells and cytokines of the epidermal immunologic unit, the frontline of immune protection against environmental toxins and microbes.

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Cutaneous immune responses involve the coordinated actions of epidermal and dermal cells along with the intricate network of cytokines. Streilein was among the first to propose a branch of the immune system specialized to provide cutaneous immunity; in 1978, he introduced the concept of skin-associated lymphoid tissues or "SALT," analogous to the gut, bronchial, or conjunctival-associated lymphoid tissues.[1] Skin-associated lymphoid tissue is an integrated system in which resident epidermal cells, keratinocytes and Langerhans cells, as well as migrant epidermotropic lymphocytes and draining regional lymph nodes, work in concert to provide the skin with immune protection against external environmental toxins, infections, and the development of cutaneous neoplasms.

Together the cells in the epidermis also serve as a vast reservoir of soluble biologic response modifiers. The cytokines produced in the epidermis allow the skin to recruit and activate a wide range of inflammatory cells. Many of these cytokines are released from the epidermis whenever the cutaneous barrier is compromised, whether by direct trauma, infections, allergens, or toxins. The local release of these cytokines and the systemic absorption through the superficial vascular plexus of the upper dermis serve as an early signal to the host immune system that the external barrier (skin) has been disrupted. In this way, the immune system can be activated, mobilized, and directed to the site of cutaneous injury and the source of secreted cytokines.*

Cellular Components of the Epidermal Immune Unit

Langerhans Cells—Epidermal Antigen-Presenting Cells

In 1868 Paul Langerhans, a medical student interested in the anatomy of cutaneous nerves, inoculated gold into human skin and discovered a population of dendritic cells in the epidermis.[2] Although originally thought to represent intraepidermal neural receptors, Langerhans cells are now recognized as the major antigen-presenting cells of the skin and play a key role as the peripheral component of the immune system. Langerhans cells are one of a large family of class II major histocompatibility complex (MHC)-bearing dendritic cells critical to antigen processing and presentation to specific T lymphocytes. Langerhans cells contain intracytoplasmic "tennis racket-shaped" organelles called Birbeck granules that appear to result from the internalization of class II MHC cell-surface molecules; the precise role of these unique granules in anti-

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ABBREVIATIONS USED IN TEXT

CLA = cutaneous leukocyte-associated antigen
ELAM = endothelial cell-leukocyte adhesion molecules
ICAM = intercellular adhesion molecule
IFN = interferon
Ig = immunoglobulin
LFA = lymphocyte function-associated antigen
MHC = major histocompatibility complex
TNF = tumor necrosis factor
V = variable gene segment of the T cell-receptor gene

gen-processing, presentation, or both is unclear.[3] These cells are capable of phagocytosis, although their efficiency at this feat is less than that of macrophages and even keratinocytes. Langerhans cells have receptors for the Fc component of immunoglobulin (Ig) G and IgE and the third component of complement (C3). These receptors may facilitate phagocytosis of antibody and complement-coated particles.[4,5]

Derived from the monocytic lineage of the bone marrow, Langerhans cells migrate to the skin to make up 2% to 4% of epidermal cells, with most taking residence in the suprabasal regions of the epidermis; a few cells may be found in the dermis, draining lymph nodes, and in the thymus.[4] In the epidermis, their long dendritic processes intercalate between keratinocytes, and although there is no evidence of physical or functional contact between dendrites, they appear to form an "immunologic net" parallel to the skin surface, efficiently trapping antigenic molecules.

In normal, noninflamed epidermis, Langerhans cells are the only cells that express a substantial level of class II MHC antigens (HLA-DP, -DR, -DQ in humans; Ia and Ie in the murine system).[6] These surface molecules are required for the stimulation of T cell-dependent immune responses. Langerhans cells play a two-tiered antigen-presenting role in the peripheral immune system: they present antigen in the context of class II MHC molecules to naive T cells in the induction of cell-mediated immunity and to memory and effector T cells in the expression of cutaneous immune responses.[7] They are critical to cutaneous antigen-specific syngeneic and allogeneic T-cell activation and the generation of epidermal cell-induced cytotoxic T cell reactions.[4,8] They are required for the induction of cutaneous delayed-type hypersensitivity responses[9] and are critical to epidermal allosensitization such as graft-versus-host reactions.[4,8] There is experimental evidence that during the sensitization or induction of a T cell-mediated immune response, Langerhans cells process exogenous antigen and form complexes with cell surface class II MHC molecules in a manner similar to that of tissue macrophages. Antigen-bearing Langerhans cells undergo certain phenotypic changes and migrate through dermal lymphatics to regional lymph nodes where they become more like the dendritic cells of lymph nodes, stimulating specific naive or primed T lymphocytes to proliferate and differentiate. The antigenic signal is transduced into an effector signal by specifically sensitized cells or antibodies; these immune effectors may then leave the lymph node and circulate in the bloodstream to the original site of antigenic stimulation, interact with specific antigen-bearing Langerhans cells, and execute an immune response. If at the time of the initial antigenic stimulation the appropriate antigen-specific lymphocytes are already in the skin, antigen recognition during the inductive phase of the immune response may take place entirely within the skin.[10]

The efficiency of these cells to function as antigen-presenting cells depends not only on the expression of cell surface class II MHC molecules but also on membrane adhesion molecules. Cellular adhesion molecules allow direct physical contact between Langerhans cells and T cells, thus facilitating their interactions and T-cell activation. Langerhans cells in vitro express adhesion molecules, such as intercellular adhesion molecule (ICAM)-1 (which is identical to CD54) and lymphocyte function-associated antigen (LFA)-3, both of which are glycoproteins of the immunoglobulin gene superfamily. Intercellular adhesion molecule-1 is the ligand for LFA-1, an integrin that is present on the surface of most hematopoietic cells and antigen-presenting cells, and LFA-3 is the ligand for CD2 (which is identical to LFA-2), a glycoprotein of the immunoglobulin gene superfamily that is present on T lymphocytes.[11,12]

Cytokines such as interleukin-1 and tumor necrosis factor (TNF)α that are produced by keratinocytes may increase class II MHC and adhesion molecule expression on Langerhans cells, thus augmenting their efficiency as antigen-presenting cells.[13] Furthermore, Langerhans cells may themselves modulate immune responses in the skin through the secretion of soluble mediators such as interleukin-1β, which can act in an autocrine and paracrine manner to promote immune responses in the skin.[14] In addition, preliminary studies suggest that Langerhans cells may express messenger RNA for interleukin-6 and macrophage inflammatory protein-1α.[5] Thus, these cells represent a key component of the host immune system responsible for initiating cutaneous cellular immune responses.

Keratinocytes—Immune-Competent Epithelial Cells

Over the past few years, the revelation that keratinocytes are immunologically active cells has reinforced the concept that the skin is an active immune organ.[1] Accounting for greater than 90% of epidermal cells, keratinocytes not only create a complex physical barrier to environmental agents but also serve as accessory cells in cutaneous immune responses. Keratinocytes may play a role in initiating cell-mediated immune responses in the skin by releasing cytokines and expressing cellular adhesion molecules to facilitate the movement of immune-competent cells.

In 1976 Edelson, who was studying cutaneous T-cell lymphoma, a disease characterized by epidermal infiltration by malignant T-helper cells, became one of the first to suggest that epidermal cells may influence T-lymphocyte migration and proliferation.[15] In 1981 Rubenfeld and

co-workers observed that epidermal cell cultures produce soluble substances that induce lymphocyte differentiation,[16] and a year later, Chu and associates discovered a keratinocyte-derived factor similar to thymopoietin.[17] During this period, Luger and colleagues, along with Sauder and co-workers, discovered and further characterized a keratinocyte-derived cytokine that was initially named epidermal cell-derived thymocyte activating factor and is now known to be identical to interleukin-1.[18-20]

It is now well established that keratinocytes constitutively synthesize the two subtypes of interleukin-1: both interleukin-1α and, to a lesser extent, interleukin-1β.[20,21] Keratinocytes lack the ability to export interleukin-1 under normal conditions but may be activated—by other cytokines—to secrete interleukin-1 or may undergo direct cell injury to allow the release of this cytokine. They may thus serve as a vast reservoir of this protein factor, synthesizing and storing the cytokine until the appropriate stimulus induces interleukin-1 secretion to initiate local and systemic inflammatory responses.[22] Interleukin-1 is a pleotropic cytokine with a broad spectrum of biologic effects, including inducing thymocyte proliferation, activating T and B cells, amplifying the immunostimulatory potential of dendritic cells, promoting monocytic cytotoxic activity against tumor cells, stimulating fibroblast mitogenesis and collagen synthesis, producing hepatic acute-phase reactants, and inducing fever. Target cells of interleukin-1 include keratinocytes, T lymphocytes, neutrophils, macrophages, fibroblasts, and smooth muscle cells. Through autocrine and paracrine actions, interleukin-1 may augment the expression of its receptors on target cells and induce keratinocytes to synthesize and secrete interleukin-1 and other cytokines. It is now recognized that "activated" keratinocytes produce at least 15 biologic response modifiers, and the list of mediators continues to grow.[22,23] This array of cytokines can mediate the wide variety of inflammatory responses observed in the skin.

In addition to cytokine production, keratinocytes may directly participate in cell-mediated immune responses by the expression of class II MHC molecules. In normal, noninflamed epidermis, keratinocytes have only class I MHC antigens on their surface and do not express class II MHC antigens (HLA-DP, -DQ, and -DR in humans). In inflamed skin, however, infiltrating T lymphocytes secrete interferon γ (IFN-γ), which is capable of activating keratinocytes to transiently express class II MHC antigens (DR).[24] The role of class II antigen-bearing keratinocytes in cutaneous immune responses has not been established. Although these activated cells do not appear capable of presenting antigen to naive T cells, some studies have suggested that they may activate memory and effector T cells. Other data suggest, however, that class II MHC-bearing keratinocytes provide signals that specifically inhibit cell-mediated immune responses in the skin.[25]

Activated keratinocytes may also influence the movement of immune-competent cells and effector cells into the skin by the expression of specific adhesion molecules such as intercellular adhesion molecule (ICAM)-1. Although keratinocytes do not constitutively express ICAM-1 (as do Langerhans cells and human dermal microvascular endothelial cells), they may be induced to express the ICAM-1 molecule by secreted IFN-γ and TNFα.[12,26] T lymphocytes that express cell surface LFA-1 may adhere to cells expressing ICAM-1 such as keratinocytes specifically by LFA-1–ICAM-1 conjugate formation. This interaction may be important in recruiting and moving immune cells to the point of antigenic stimulation or skin injury.[12,27] For example, during allergic contact hypersensitivity reactions, ICAM-1 expression on keratinocytes temporally correlates with the dermal infiltration of mononuclear cells and the development of clinical dermatitis.[28] Keratinocyte ICAM-1 expression is also increased in psoriatic skin lesions and correlates with a dense mononuclear infiltrate; treatment with methoxsalen (8-methoxypsoralen) and ultraviolet A results in a pronounced decrease in ICAM-1 expression on keratinocytes that parallels a reduction in the mononuclear dermal infiltrate and clinical improvement.[29] Keratinocyte ICAM-1 expression in juxtaposition with epidermotropic LFA-1-expressing T lymphocytes has been described in a number of other inflammatory dermatoses, such as lichen planus, and in cutaneous cancers, namely the early stages of cutaneous T-cell lymphoma, also known as mycosis fungoides.[30] In addition, under the stimulation of IFNγ, human keratinocytes may secrete soluble ICAM-1 molecules that can bind to LFA-1 and possibly competitively block LFA-1-mediated cellular interactions. Because some malignant keratinocytic lines have been shown to constitutively synthesize soluble ICAM-1 (without cytokine stimulation), some have speculated that soluble ICAM-1 may provide a mechanism by which these neoplastic cells may escape from immunologic cytotoxicity.[31]

Dendritic Epidermal T Cells—Specialized Resident Epithelial T Cells

In 1983 Tschachler and Bergstresser and associates independently described a population of dendritic epidermal T cells that express Thy-1 cell surface glycoprotein but lack class II MHC antigen.[32,33] Also known as Thy-1$^+$ dendritic epidermal cells, dendritic epidermal T cells are a unique subset of epidermotropic bone marrow-derived cells that have been best defined in mice. To date, a precise equivalent in human skin has not been described. Residing in the basal layer of the epidermis as a relatively sessile, dendritic population of cells distinct from melanocytes and Langerhans cells, dendritic epidermal T cells make up 0.8% to 2% of murine epidermal cells.[34,35]

The phenotypic features of dendritic epidermal T cells are intriguing: they share with immature thymocytes the Thy-1 alloantigen, CD45, and CD3 antigens as well as the neutral glycolipid asialo-Gm-1 antigen, which is a marker for natural killer cells but may also be present on thymocytes and certain peripheral T cells.[32,33,35,36] Dendritic epidermal T cells lack mature peripheral T-cell markers such as CD5 and CD4, and most of these cells also lack CD8 antigens.[32,37] Like immature thymocytes, the CD3 antigens of dendritic epidermal T cells are predominantly associ-

ated with T-cell receptor γ/δ heterodimers rather than the α/β heterodimers that are present on most peripheral T cells.[34,38] Antigen recognition by dendritic epidermal T cells is not restricted by conventional polymorphic class I or class II MHC molecules but instead appears to be restricted by relatively nonpolymorphic self-MHC-like molecules of the class Ib MHC type.[35] In addition, dendritic epidermal T cells are characterized by limited T cell-receptor diversity: the cells selectively express variable (*V*) gene segments and display restricted γ/δ pairing such that the epitopes of dendritic epidermal T-cell receptors in the epidermis are predominantly *V*γ3 and *V*δ1.[34,39] The limited expression of *V*γ and *V*δ genes, the lack of CD4 and CD8 antigens, and the early appearance of γ/δ cells during murine ontogeny suggest that these cells may represent a phylogenetically "primitive" immune defense system.[35]

The specific function of this unique subset of epidermal T cells has eluded investigators. These epidermal T cells may participate in cutaneous immune surveillance, possibly by cytotoxic activities against foreign or altered-self target cells. In vitro, interleukin-2–stimulated dendritic epidermal T cells gain natural killer-like cell properties and mediate non-MHC-directed cytotoxicity.[36] These epidermal T cells may also secrete immunologic cytokines such as interleukin-2.[35,39] Some studies suggest that they may also play a role in the induction of tolerance. Hapten-conjugated dendritic epidermal T cells injected into a mouse footpad do not elicit contact hypersensitivity but instead induce antigen-specific tolerance that does not require the recognition of polymorphic self-MHC molecules. Because of the cytotoxic potential of these cells, some investigators have suggested that hapten-conjugated dendritic epidermal T cells may bind to T-helper cells (which express a hapten-specific receptor) and induce tolerance by killing these T-helper cells in a non-MHC-restricted manner.[40] Other studies, however, have not uniformly demonstrated the induction of tolerance after the subcutaneous administration of hapten-conjugated epidermal T cells, possibly because of different study designs and techniques.[41]

Another interesting theory regarding dendritic epidermal T-cell function takes into consideration the limited diversity of their γ/δ receptors, which, as mentioned, suggests a narrow range of ligands. Asarnow and co-workers have proposed that the mammalian heat-shock proteins may serve as a common ligand for these cells.[38] Heat-shock proteins are a highly conserved family of molecules that can be expressed by cells after a variety of insults, such as heat, hypoxia, ultraviolet radiation, γ-irradiation, viral infection, and malignant transformation.[35] Furthermore, cells infected with various species of mycobacteria can produce proteins that are homologous to mammalian heat-shock proteins.[35,42] Thus, it is possible that the relatively homogeneous receptors of dendritic epidermal T cells recognize and respond to a number of physical and chemical stresses that have been transformed into a common antigenic stimulus, that is, heat-shock (or related) proteins.

In humans, cells equivalent to murine epidermal T cells have not been found, although some distinct subsets of T lymphocytes share some of their features. These subsets include nondendritic γ/δ T cells and "double-negative" ($CD4^-CD8^-$) α/β T cells. Although most T lymphocytes in humans express the α/β-antigen receptor, 1% to 15% of intraepidermal and dermal T lymphocytes express the γ/δ-antigen receptor. Like murine dendritic epidermal T cells, human γ/δ T cells usually lack the CD4 and CD8 antigens and are capable of a non-MHC-restricted recognition of tumor targets. Human γ/δ T cells also recognize some specific antigens such as heat-shock proteins and mycobacterial antigens.[34,43]

Similar to most human γ/δ T cells and murine dendritic epidermal T cells, a few α/β T cells described in both humans and mice lack both CD4 and CD8 antigens (in contrast to the vast majority of α/β T cells that express either the CD4 or CD8 antigens). Like murine epidermal T cells, these "double-negative" α/β cells display non-MHC-restricted cytotoxicity against several tumor targets. Double-negative α/β T cells in mice display restricted expression of the *V*b-gene region; further studies are needed to characterize the degree of T cell-receptor diversity in human α/β $CD4^-CD8^-$ T cells.[44]

Unlike murine dendritic epidermal T cells, human γ/δ T cells and double-negative α/β T cells lack a dendritic structure and do not appear to selectively home to epithelial tissues. Nevertheless, the shared phenotypic features with epidermal T cells and the possible functional similarities are intriguing. These unique T-cell subsets, functioning in a manner distinct from MHC-restricted immune pathways, may provide an early defense network against a variety of insults, such as mycobacterial and other infections, tumor cells, and so on, by a common antigenic stimulus, such as heat-shock proteins.

Epidermotropic T Lymphocytes—Circulating T Cells That Home to the Epidermis

Circulating skin-homing lymphocytes are crucial to the initiation and execution of cutaneous immune responses. In normal human skin, all extravascular lymphocytes are of the T-cell type. Most of these T cells express the α/β-antigen receptor in contrast to the previously discussed γ/δ receptors expressed on murine dendritic epidermal T cells. The perivascular or periadnexal areas in the dermis contain 90% of the cutaneous T lymphocytes. These dermal T lymphocytes comprise an approximately equal number of $CD4^+$ inducer and $CD8^+$ suppressor or cytotoxic lymphocytes; of the $CD4^+$ T cells, most are $CD4^+$ $4B4^+$ helper or inducer cells, whereas less than 5% are $CD4^+$ $2H4^+$ suppressor-inducer T lymphocytes. The vast majority of dermal lymphocytes are in the activated state (express HLA-DR and interleukin-2 receptors). Less than 2% of T lymphocytes in the skin are within the epidermis where they make up 0.16% of epidermal cells; virtually all intraepidermal T lymphocytes are $CD2^+$, $CD3^+$, $CD8^+$ suppressor-cytotoxic T lymphocytes.[45] That the composition of the lymphocytic infiltrates within the skin does not mirror their concentrations in the peripheral

bloodstream supports the concept of nonrandom migration of lymphocytes into the skin and T-cell "homing."[1]

Intercellular adhesion molecules expressed on dermal endothelial cells may mediate leukocyte adhesion, migration through vessel walls, and trafficking into the dermis and epidermis. T lymphocytes can adhere to both endothelial cells and keratinocytes specifically by LFA-1–ICAM-1 conjugate formation. Endothelial cells constitutively express low levels of ICAM-1 and can be induced to express increased levels of ICAM-1 by interleukin-1, TNFα, and IFN-γ.[46,47] As described earlier, IFN-γ and TNFα may also induce ICAM-1 expression on keratinocytes, and T-cell migration to the epidermis may be inhibited by antibodies directed against LFA-1 and ICAM-1.[12,26,48]

Endothelial cell-leukocyte adhesion molecule (ELAM)-1 and cutaneous lymphocyte-associated antigen may compose another receptor-ligand pair that directs the movement of T lymphocytes to the skin.[49,50] Endothelial cell-leukocyte adhesion molecule-1 is a member of the "LEC-CAM" or "selectin" family of cell adhesion molecules. Although it may be present on inflamed endothelial cells of nearly any tissue, its expression is particularly prominent on inflamed endothelial cells of the skin.[49] Soluble mediators of inflammation such as TNFα may increase the expression of ELAM-1 on endothelial cells.[51] Neutrophils bear the sialylated Lewis x determinant, which can serve as a ligand for ELAM-1; the ligand on T cells has not yet been identified but may be the cutaneous lymphocyte-associated antigen (CLA). (This is not to be confused with the common leukocyte antigen, CD45, a marker present on a specific subset of memory T cells.[49,50,52]) Some investigators have proposed that ELAM-1 may serve as a "skin vascular addressin," a tissue-selective endothelial cell adhesion molecule for skin-homing memory T cells.[49,50]

During the efferent phase of cutaneous immune responses, memory and effector T cells (generated in the regional lymph nodes that drain the original site of antigen exposure) circulate in the bloodstream; meanwhile, at the site of antigenic stimulation, cytokines, such as IFN-γ and TNFα, are released and increase ICAM-1 and ELAM-1 expression on endothelial cells. These adhesion molecules serve as recognition signals for leukocytes that express LFA-1, CLA, or both. Through conjugate formation between LFA-1 and ICAM-1 and CLA and ELAM-1, memory and effector cells may be efficiently targeted to the site of antigen exposure or skin injury.

Melanocytes—Epidermal Pigment Cells With Immune Properties

Although melanocytes have been traditionally considered to have no immunologic role, recent findings suggest that these cells may contribute to the immune function of the epidermis by secreting biologic response modifiers. Melanocytes represent 2% to 5% of epidermal cells; the number of melanocytes varies from person to person and in different anatomic sites of the same person. Like Langerhans cells, they possess numerous dendritic processes and are strategically placed in the lower epidermis, close to the dermis, where they may play important roles in immune responses.[53]

Melanocytes produce a number of cytokines that may mediate inflammation in the epidermis and dermis. Melanocytes constitutively produce interleukins-1, -3, and -6, granulocyte-macrophage colony-stimulating factor, TNFα, and transforming growth factor β[54-58] and, after exposure to specific cytokines or neuropeptides, can increase the production of these cytokines and secrete interleukin-8 and monocyte chemotactic and activating factor.[53] Cultured melanocytes may produce both interleukin-1α and β and, unlike keratinocytes, contain a convertase enzyme that transforms the inactive 33-kd interleukin-1β to the active 17-kd product. Some investigators have suggested that the melanocyte-derived interleukin-1β convertase may act on the 33-kd interleukin-1β produced by keratinocytes to create an active mediator.[54,55]

Cytokines may have other autocrine and paracrine actions on melanocytes, influencing their growth, migration, enzymatic (tyrosinase) activity, and their expression of adhesion molecules, which are critical to cell-cell interactions. Although human melanocytes do not constitutively express adhesion molecules, IFN-γ, TNFα and β, interleukins-1α, -6, and -7 may induce ICAM-1 expression on melanocytes (depending on culture conditions).[59,60] Future studies will elucidate the nature of the interactions between melanocytes and other cells of the immune system.

Summary

It is clear that the epidermis can function as an immunologic tissue. This is critically important to its function as a barrier to external toxins and microbes. In this review, we have focused on the major immune-competent cells of the epidermis. To recapitulate, one of the first cells to encounter toxins or antigens in the skin are the macrophage-like Langerhans cells. As the major antigen-presenting cells of the epidermis, Langerhans cells play a critical role in both the afferent and efferent limbs of the cutaneous immune system. Parenchymal cells, most of which are keratinocytes, serve as accessory cells in cutaneous immune responses. As a reservoir of preformed interleukin-1, keratinocytes may function as an early warning system, releasing this cytokine after cellular injury or cytokine activation. Interleukin-1 may then exert a multitude of local and systemic effects, acting directly on cells and indirectly through the modulation of cytokine production. Moreover, it acts on all of the key components of the cutaneous immune system: interleukin-1 increases cytokine production of keratinocytes and induces class II MHC antigen and ICAM-1 expression on keratinocytes; it augments the immunostimulatory potential of Langerhans cells by enhancing their expression of class II MHC antigen; it also increases the expression of adhesion molecules on dermal endothelial cells, further facilitating leukocyte trafficking into the skin; furthermore, interleukin-1 is chemotactic for T lymphocytes and promotes their production of and respon-

siveness to cytokines. In murine epidermis, dendritic epidermal T cells may represent a primitive immune surveillance system of epithelial tissues. Another possible component of the cutaneous immune system is melanocytes, which may serve as accessory cells by secreting soluble mediators of inflammation.

Although we have focused on the epidermal immune unit, we recognize that the epidermis interacts substantially with the underlying dermis, which is populated with immune-competent cells and soluble inflammatory mediators. Recent advances in immunodermatology have illuminated the complexity of this amazingly effective and efficient physical and immunologically active barrier. With the powerful tools of molecular biology available, new dimensions are continually being added to these concepts as we expand our understanding of the skin as an immune organ and explore new therapies for cutaneous disease.

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TRIPLE BYPASS

I hide my face though cybernetic dreams
surround me like sentinels on parade.

Technical hobgoblins call it pericardium
for me the gates of heaven unveil and I

divine celestial majesty pulsating
with rhythmic hymns of life and glory.

If God lives he lives below the sixth rib among
conical truths echoing the heckles of a human heart.

JONATHAN MARK BERKOWITZ©
Bryn Mawr, Pennsylvania

Why Are Low-Density Lipoproteins Atherogenic?

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Low-density lipoproteins (LDLs) carry most of the cholesterol in human plasma, and high levels of LDL cholesterol clearly cause heart disease. In recent years, many scientists have focused on elucidating the pathophysiologic steps that lie between elevated levels of LDL in the plasma and atherosclerotic plaques in the arterial wall. A large number of scientific studies indicate that oxidation of LDL within the arterial wall may be an important early step in atherogenesis. The uptake of oxidized LDL by macrophages is a likely explanation for the formation of macrophage foam cells in early atherosclerotic lesions. In addition, oxidized LDL has many other potentially proatherogenic properties.

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Low-density lipoproteins (LDLs) are spherical particles consisting largely of cholesteryl ester, phospholipid, and a single large protein, apolipoprotein (apo) B-100. The LDL particles, which contain about two thirds of the cholesterol in healthy human plasma, are derived from the metabolism of the triglyceride-rich very-low-density lipoproteins (VLDLs). Genetic, pathologic, and epidemiologic studies, studies using animals, and dietary and drug intervention trials using human subjects have implicated high plasma levels of LDLs in the pathogenesis of atherosclerosis.[1]* In recent years, important advances have been made in understanding why these spherical lipid-protein particles are atherogenic. A pathologic hallmark of atherosclerosis is the accumulation of lipids within the macrophages of the arterial wall. There is little doubt that the lipids within the macrophage foam cells of atherosclerotic fatty-streak lesions are derived from the circulating lipoproteins. What are the steps that lead to the uptake of lipoproteins by cells in the arterial wall? Laboratory investigations have indicated that native LDL particles, such as those that circulate in the plasma, are taken up slowly by macrophages; thus, they probably have only a limited capacity to contribute to atherosclerotic foam cell formation.[2] Accumulating evidence, however, suggests that a variety of cell types within the arterial wall can oxidize LDLs and that oxidative modification alters the biologic properties of LDL, converting these lipoproteins into a form that is taken up avidly by macrophages.[3] Thus, LDL oxidation may be important in the development of foam cell lesions in the arterial wall. In addition, oxidized LDL has other properties that appear to be important in the pathogenesis of atherosclerosis.[3] In this brief review we will summarize some of the recent research indicating the role of oxidized LDLs in the pathogenesis of atherosclerosis.

*See also the editorial by A. Chait, MD, "Low-Density Lipoprotein and the Pathogenesis of Atherosclerosis," on pages 183-184 of this issue.

What Are Low-Density Lipoproteins, and Where Do They Come From?

Low-density lipoproteins have a diameter of about 22 nm and a hydrated density ranging from 1.019 to 1.063 grams per ml. The core of the LDL particle consists largely of cholesteryl ester, with a small amount of triglycerides. The surface coat of LDL consists of phospholipids—mainly phosphatidylcholine and sphingomyelin—free cholesterol, and a single molecule of a large protein, apo B-100.[4] The fatty acids of the LDL phospholipids reflect, to an extent, the fatty acids consumed in the diet.[5] The most abundant fatty acid in human LDL is the polyunsaturated fatty acid, linoleate (18:2).[5] Apolipoprotein B-100, which is 4,536 amino acids in length, has numerous sequences throughout its length that are thought to be important in lipid binding.[6] The apo B-100 polypeptide chain is thought to "circumnavigate" the LDL sphere,[7] and it has been speculated that numerous short hydrophobic segments of the apo B molecule "dive" in and out of the neutral lipid core of the particle.[8]

Low-density lipoproteins are the product of the metabolism of triglyceride-rich VLDLs, which are synthesized and secreted into the plasma by the liver.[4] The triglyceride core of the VLDL is hydrolyzed by lipopro-

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ABBREVIATIONS USED IN TEXT

apo = apolipoprotein
HDL = high-density lipoprotein
LDL = low-density lipoprotein
VLDL = very-low-density lipoprotein
WHHL = Watanabe heritable hyperlipidemic [rabbits]

tein lipase, which is located along the capillary endothelium, principally in muscle and adipose tissue. As the triglyceride core of VLDL particles shrinks, the excess surface components of VLDL (including free cholesterol, several small apolipoproteins, and phospholipids) are transferred to the high-density lipoproteins (HDLs); at the same time, cholesteryl esters are transferred from the HDL to the VLDL remnant. Most of the cholesteryl ester in VLDL remnants is derived from the HDL. About half of VLDL particles are removed from the circulation in the liver by specific receptors on the hepatocyte cell membrane.[4] The remainder of VLDL is gradually metabolized in the circulation to smaller, denser, cholesteryl ester-rich particles of the LDL class. The final processing of VLDL remnants to LDL involves processing by another lipolytic enzyme, hepatic lipase. The residence time of LDL in the circulation is normally two to three days. About three fourths of LDL particles are removed by the liver and the remainder by extrahepatic tissues.[9] Most of the uptake of LDL by cells is mediated by a specific cellular receptor, the LDL receptor.[10] The apo B-100 on LDL particles is a ligand for the LDL receptor and mediates the binding and uptake of LDL by cells.[11]

Evidence That High Plasma Levels of Low-Density Lipoprotein Cause Atherosclerosis

Perhaps the best evidence that LDL is atherogenic comes from two monogenic inherited metabolic disorders that cause high plasma LDL levels. In familial hypercholesterolemia, the cellular LDL receptor is either absent or structurally altered so that it cannot bind and internalize LDL.[10] As a result of this genetic defect, LDL cannot be taken up by cells at a normal rate and therefore accumulates in the plasma. In familial defective apo B-100, a single amino acid substitution in apo B-100 interferes with the high-affinity binding of LDL–apo B-100 to the LDL receptor.[12] The metabolic consequences of this defect are virtually identical to those observed with LDL-receptor defects—an accumulation of LDL in the plasma. Affected heterozygotes for either genetic disorder have high LDL-cholesterol levels (> 4.90 mmol per liter [190 mg per dl]), tendon xanthomas, and premature coronary atherosclerosis.[10,13,14] Thus, two different gene defects, each having the primary effect of raising LDL levels, cause premature atherosclerosis.

In addition to genetic evidence implicating LDLs in the pathogenesis of atherosclerosis, many observational, epidemiologic, and cross-cultural studies have shown a strong association between elevated LDL levels and atherosclerotic heart disease.[14] Furthermore, experimental studies with nonhuman primates have demonstrated that cholesterol-rich and saturated fatty acid-rich diets (which elevate plasma LDL levels) result in foam cell-rich atherosclerotic lesions in the aorta and coronary arteries; stopping these atherogenic diets results in the reversal of atherosclerosis.[15-17] In humans, drug therapy specifically designed to lower LDL-cholesterol levels prevents the development of coronary heart disease in healthy hypercholesterolemic subjects[14,18,19] and improves coronary artery anatomy in those with already established atherosclerotic disease.[20-24] Thus, the evidence proving that elevated LDL levels are causally related to atherosclerosis is extremely strong and essentially incontrovertible.

Metabolic Changes in Low-Density Lipoproteins Produced by Chemical Modification

With the link between elevated LDL levels and atherosclerosis firmly established, many investigators of lipoprotein metabolism have shifted their efforts from determining whether or not LDLs are atherogenic to trying to understand *why* LDLs are atherogenic. An important insight into the mechanism of LDL atherogeneity was made by the laboratory of Brown and Goldstein.[2,25] They recognized, clearly articulated, and experimentally explored a seemingly paradoxical set of observations. The first observation was that elevated levels of LDL in the plasma led to the development of atherosclerotic fatty-streak lesions containing macrophage foam cells. The second observation was that in both humans and animals with genetic defects in the LDL receptor, typical atherosclerotic lesions develop that are rich in macrophage foam cells despite the absence of functional LDL receptors; this strongly implies that the LDL receptor does not mediate the uptake of lipoproteins into foam cells. The third observation was that normal monocyte-derived macrophages have an extremely limited capacity to take up and degrade freshly isolated LDL.

The question that naturally arises from these observations is, What mechanism accounts for the uptake of LDL into macrophage foam cells in the arterial wall? As reported in a landmark article,[25] a chemical modification of LDL was found with acetic anhydride (which acetylates the ϵ amino group of lysine residues of apo B, thereby increasing the negative charge of LDL) that dramatically alters the intrinsic metabolic properties of the LDL. Unlike normal LDL, the acetylated LDL (acetyl LDL) could not bind to the LDL receptor on cultured fibroblasts. The acetyl LDL was, however, taken up and degraded by cultured monocytes or macrophages through the action of a cellular receptor—which Goldstein and co-workers designated the scavenger receptor—distinct from the LDL receptor. The uptake of acetyl LDL by cultured macrophages was saturable and extremely rapid; macrophage foam cells could be produced in cell culture overnight by incubating the cells with acetyl LDL. Unlike the LDL receptor, the activity of the scavenger receptor could not be inhibited by incubating the macrophages with sterols. The scavenger receptor also recognized a variety of other lig-

ands, including acetoacetylated LDL, malondialdehyde-modified LDL, polyinosinic acid, and other polyanionic compounds.[2] A cell membrane receptor that was capable of binding acetyl LDL—designated the acetyl-LDL receptor—has been purified and its primary structure determined.[26-29]

The biologic relevance of acetyl LDL produced by chemical modification of LDL was not clear initially because substantial amounts of acetylation of plasma proteins do not occur in vivo.[2] In 1981, however, Henriksen and associates reported that cultured endothelial cells have the capacity to biologically modify LDL in such a way that it could be taken up rapidly by cultured macrophages.[30] Like chemically acetylated LDL, the endothelial cell-modified LDL had an increased negative charge. Cell culture studies revealed that this modified LDL could compete with acetyl LDL for uptake by the acetyl-LDL receptor of macrophages, indicating that it binds to the same receptor.[30,31] The observation that endothelial cells could biologically modify LDL was of immediate interest because it posed a plausible hypothesis for how LDL might be taken up in vivo by macrophage foam cells in the arterial wall. Subsequent cell culture studies of LDL modification have shown that each principal cell type found in the arterial wall—endothelial cells, smooth muscle cells, macrophages, and fibroblasts—have the capacity to modify LDL so that these lipoproteins are taken up rapidly by cultured macrophages.[3,32] Furthermore, in situ hybridization and immunocytochemistry studies have shown that macrophages in the arterial atherosclerotic lesions (but not cells of nonlesioned regions of the artery wall) express the acetyl-LDL receptor—the receptor that recognizes biologically modified LDL.[3,33,34] In contrast, the arterial macrophage foam cells express little LDL receptor.[34] The acetyl-LDL receptor has also been identified in rabbit smooth muscle cells by the laboratory of Pitas.[35]

Nature of the Biologic Modification of Low-Density Lipoprotein by Cells

Studies at the University of California, San Diego,[30,36] and other laboratories[37] have shown that the biologic modification of LDL by cultured endothelial cells involves oxidation of the polyunsaturated fatty acids in the low-density lipids and that this modification reaction can be largely or completely inhibited by antioxidants such as butylated hydroxytoluene or vitamin E.[3,38] Oxidative modification of LDL by cultured cells is absolutely dependent on small concentrations of copper or iron and can be inhibited by divalent metal chelators such as edetate. The oxidation of LDL requires the free radical-mediated abstraction of a hydrogen atom of a polyunsaturated fatty acid, forming a fatty acid radical, that then can react with oxygen to form lipid hydroperoxides.[32] The initial peroxides or radicals can react with antioxidants contained within LDL, such as vitamin E, and thereby lose their ability to produce oxidation; an LDL particle that is sufficiently enriched in antioxidants is resistant to oxidative modification.[39] Once the antioxidants are depleted, however, the lipid hydroperoxides can be a source of further free radicals by ferric or cupric ion catalyzed reactions, leading to an acceleration of polyunsaturated fatty acid peroxidation. The speed and extent of fatty acid peroxidation is dramatically increased by phospholipase A_2 activity, which is intrinsic to the LDL particle and may be specified by some part of the apo B-100 molecule.[39,40] It seems likely that this phospholipase activity specifically acts on oxidized phospholipids at the surface of LDL, thereby liberating fatty acid hydroperoxides and allowing them to disperse throughout the LDL particle, accelerating the oxidation reaction. Inhibitors of phospholipase A_2 such as *p*-bromophenacyl bromide dramatically inhibit LDL oxidation.[40] The phospholipase activity within LDL is responsible for an increased content of lysolecithin in oxidized LDL. Similar to the use of cultured cells, LDLs can be oxidized in vitro simply by incubating them with low concentrations of cupric or ferric ions.[32]

The mechanism for initiating LDL oxidation by cultured cells is not understood in detail and requires further study. Some investigators think that the oxidation of polyunsaturated fatty acids is initiated by the secretion of superoxide anions, which are eventually capable of generating highly reactive hydroxyl radicals that can attack polyunsaturated fatty acids to form fatty acid hydroperoxides.[41] Other evidence suggests that superoxide anions may have only a secondary role in LDL oxidation.[42] Another possibility for the oxidation of LDL is that a cellular enzyme, 15-lipoxygenase, generates fatty acid hydroperoxides, which could be incorporated into the cell membrane, where they could interact with extracellular LDL, or could leave the cell, where they might interact directly with LDL.[32,42] In the presence of divalent metal ions, fatty acid hydroperoxides can lead to a rapid oxidation of LDL fatty acids. Sparrow and associates have shown that a purified soybean lipoxygenase can oxidize LDL effectively, particularly when a phospholipase A_2 is included in the reaction.[43] Cell-generated cysteine, through cellular cysteine recycling, has also been suggested to have an important role in the generation of extracellular free radicals.[44] At present, it is generally thought that different cell types may contribute to the oxidation of LDL by one or more mechanisms, and miscellaneous factors including cytokines and cell activation may influence the rate of cell-induced oxidation of LDL.

Oxidation results in a number of chemical changes, in both the lipid and protein moieties of LDL.[36] During the oxidation of LDL by cultured cells or by incubation with low concentrations of cupric ions, the apo B molecule becomes fragmented[36]; frequently little or no full-length apo B-100 can be detected in oxidized LDL preparations. The fragmentation is almost certainly the result of an oxidation reaction, since it cannot be blocked by various inhibitors of proteolysis.[45] In addition, several amino acids are susceptible to oxidation. In particular, there is a considerable loss of lysines, histidines, methionines, prolines, and cysteines. Oxidation of LDL also leads to a striking depletion of polyunsaturated fatty acids.[46] In contrast, monounsaturated fatty acids such as oleic acid (18:1) are

not as susceptible to oxidative degradation and may actually retard the oxidative modification of LDL when they are present in LDLs in sufficiently high concentrations.[47] (Resistance of oleic acid to oxidation offers an attractive scientific basis for the beneficial effects of a "Mediterranean" diet in protecting against coronary artery disease.[5]) Low-density lipoprotein sterols also undergo oxidation; the most abundant oxidized sterols are 7-ketocholesterol, 7-hydroxycholesterol, hydroperoxycholesterol, and 5,6-epoxycholesterol.[48-50]

The effects of oxysterols on cellular metabolism have not been studied in detail. It has been suggested that some of the oxidized cholesterol derivatives may affect the acyl-coenzyme A:cholesterol acyltransferase reaction, thus accounting for the decreased esterification of cholesterol when oxidized LDL is incubated with macrophages.[49,50] In addition, the peroxidation of the polyunsaturated fatty acids of LDL leads to the production of a large number of highly reactive ketones and aldehydes, including malondialdehyde, hexanal, and 4-hydroxynonenal.[46] Either the fatty acid hydroperoxides themselves[51] or the fatty acid breakdown products[3] covalently react with the ϵ amino groups of lysine residues in apo B; consequently, the lysine content of the apo B of oxidized LDL is considerably lower than is observed in the apo B of normal LDL.[52] Derivatization of the apo B lysines by-products of LDL oxidation almost certainly accounts for the increased negative charge of oxidized LDL and for the ability of oxidized LDL to bind to the scavenger receptor. Parthasarathy and colleagues have successfully solubilized the derivatized and fragmented apo B from delipidated oxidized LDL and have demonstrated that it competes with acetylated LDL for binding to the acetyl-LDL receptor.[53] Also, LDL modified in vitro with malondialdehyde[54,55] competes with acetyl LDL for uptake by the acetyl-LDL receptor. Strongly oxidized LDL preparations no longer have the capacity to bind to the LDL receptor, undoubtedly because of the extensive fragmentation and derivatization of apo B. A summary of the important chemical, physical, and intrinsic metabolic properties of oxidized LDL is shown in Table 1.

The neutral lipid core and surface coat of LDL contain several lipid-soluble antioxidants, including β-carotene, α-tocopherol, γ-tocopherol, lycopene, ubiquinol, and other compounds. On a molar basis, however, LDL contains several hundredfold more molecules of polyunsaturated fatty acids than these natural antioxidants.[46,56,57] In vitro studies of the oxidation of LDL have demonstrated that these natural antioxidants protect LDL from fatty acid peroxidation for only a short period. Following a "lag time" during which the antioxidants are consumed, the destruction of polyunsaturated fatty acids proceeds rapidly, along with the fragmentation of apo B and the covalent modification of apo B molecules. There is heterogeneity in the lag time preceding LDL oxidation with LDL specimens from different persons,[58-60] as well as in the extent of oxidation of LDL specimens from different persons. This heterogeneity has been seen even when the oxidation reactions are carried out under standardized conditions,[38] apparently reflecting different antioxidant contents of different LDL specimens. The fatty acid composition of the LDL may also play an important role in the susceptibility of LDL to oxidation.[5,47]

TABLE 1.—*Selected Properties of Oxidized (or Endotheliol Cell-Modified) Low-Density Lipoprotein (LDL)*

↑ Negative charge
↑ Density
↓ Uptake by the LDL receptor
↑ Uptake by scavenger receptors
↓ Vitamin E, β-carotene, and other antioxidants
↓ Polyunsaturated fatty acids
↓ Phosphatidylcholine and ↑ lysophosphatidylcholine
↑ Cholesterol oxidation products
↑ Hydroxy fatty acids and carbonyl compounds
Apo B-100 fragmented
Amino acids oxidized and histidine, lysine, and proline residues lost
↑ Lipid and protein fluorescence
↑ Tendency to form aggregates
↑ = increased, ↓ = decreased

Oxidation of LDL is not a simple chemical reaction, and oxidized LDL is not a simple, homogeneous substance. Many different experimental protocols for generating oxidized LDL have been reported, and the degree of oxidation of the lipids and the amount of derivatization of apo B vary widely with different oxidation protocols.[38] For example, only minimal physical and chemical changes related to oxidation are produced by a prolonged storage of LDL with oxygen or by incubation with low concentrations of copper ions.[61] Low-density lipoprotein with low degrees of oxidation, frequently called minimally modified LDL, has little apo B fragmentation, no loss of the capacity to bind to the LDL receptor, and no ability to bind to the scavenger receptor. Minimally modified LDL nevertheless has biologic properties that may be important in leading to the early development of atherosclerotic lesions (discussed later). On the other hand, profound physical, chemical, and metabolic alterations in LDL can be produced by incubating the LDL with higher concentrations of copper or with cultured cells.[32] Aside from the fact that different oxidized LDL preparations may differ in their propensity to undergo oxidation, various investigators have used different types of operational assays for assessing LDL oxidative changes.[38] When attempting to interpret the reported biologic effects of oxidized LDL, it is important to take into account these different oxidation protocols and experimental methods for assessing oxidation and the heterogeneity in the susceptibility of various LDL preparations to oxidation (even those prepared by the same laboratory under standardized conditions).[38]

Evidence That Oxidized Low-Density Lipoproteins Exist In Vivo

Laboratory studies have shown that it is difficult to oxidize LDL in the presence of either serum or plasma.[3] This finding is probably related to the presence of many

different antioxidant compounds in plasma; in addition to lipid-soluble antioxidants, other plasma components, including ascorbate, uric acid, albumin, bilirubin, transferrin, and ceruloplasmin, have antioxidant properties.[56] Because of these high concentrations of antioxidants, oxidation of LDL probably cannot occur to an appreciable extent within the plasma compartment. Cell-mediated oxidation could conceivably occur in a sequestered microenvironment within the arterial wall, where the concentration of antioxidants is lower.[3] Over the past five years, increasing evidence has indicated that the oxidation of LDL can and does occur within the arterial wall.

One of the main reasons to think that oxidation occurs within the arterial walls comes from the examination of lipoproteins extracted from lesioned areas of human arteries and the arteries of Watanabe rabbits with heritable hyperlipidemia (WHHL). (These rabbits have a structurally abnormal LDL receptor[62] and have pronounced hypercholesterolemia and accelerated atherosclerosis.[63]) Ylä-Herttuala and co-workers obtained fresh human aortas from organ donors and gently extracted and then concentrated the lipoproteins from the intima of atherosclerotic lesions.[64,65] The lipoproteins isolated from lesions of human aortas had many of the same chemical and physical properties as those of oxidized LDL prepared by incubating with cultured cells or with copper ion. These properties included an increased electrophoretic mobility (increased negative charge), fragmentation of apo B, increased density, increased lysolecithin content, and a decreased content of polyunsaturated fatty acids.[62,63] In addition, the lesion LDL had a markedly increased ability to be taken up and degraded by cultured macrophages, and this increased rate of uptake and degradation could be competed for by oxidized LDL and other ligands for the acetyl-LDL receptor. Hoff and O'Neil prepared LDL from lesions of human aortas obtained at autopsy and generally found physical and chemical alterations in the lesion LDL that were similar to those identified by Ylä-Herttuala and associates.[64-66] In addition to documenting that the LDL had an increased electrophoretic mobility and increased rate of uptake by the scavenger receptor, they found that the lesion LDL had increased fluorescence emission (420 to 450 nm, excitation at 360 nm), which is characteristic of Schiff-base adducts formed by the products of lipid oxidation and the lysines on apo B.[66]

There is also immunochemical evidence for LDL oxidation. Investigators at the University of California, San Diego, have shown that monoclonal and polyclonal antibodies can be developed that are highly specific for chemically modified lysine residues, including the chemical modifications of lysines that occur during LDL oxidation.[67,68] For example, they have developed antibodies against lysine residues that have been modified by either malondialdehyde or 4-hydroxynonenal, two aldehydes that are formed during the breakdown of polyunsaturated fatty acids. Both Ylä-Herttuala and colleagues and Hoff and O'Neil have used these immunochemical reagents to characterize the LDL isolated from atherosclerotic lesions.[64-66] Both groups found that this LDL increased in reactivity with antibodies specific for malondialdehyde-modified lysine residues. Further support for the existence of oxidation in the arterial wall has come from studies of Rosenfeld and co-workers on the properties of macrophages within atherosclerotic lesions.[69] They generated atherosclerotic lesions in the aortas of rabbits by balloon de-endothelialization followed by diet-induced hypercholesterolemia. They purified macrophage foam cells from the aortic lesion and demonstrated that these cells showed positive immunoreactivity to polyclonal and monoclonal antibodies directed against malondialdehyde- and 4-hydroxynonenal-modified LDL. These macrophages also degraded oxidized LDL by the acetyl-LDL receptor pathway. Furthermore, these cells had the capacity to oxidize LDL in vitro.[69]

Immunohistochemical studies have also provided support for the proposition that LDL is oxidized within atherosclerotic lesions. Haberland and colleagues prepared a monoclonal antibody specific for malondialdehyde-derivatized lysines and used it to look for evidence of malondialdehyde-modified proteins in atherosclerotic lesions of WHHL rabbits.[70] They found that this antibody strongly stained the extracellular matrix surrounding macrophage foam cells and that this staining colocalized with immunostaining with an apo B-100-specific monoclonal antibody. Subsequently, Palinski and associates also showed staining of rabbit arterial lesions by antibodies specific for oxidized LDL, malondialdehyde-modified LDL, or 4-hydroxynonenal-modified LDL.[68] Moreover, these antibodies stained both extracellular areas and macrophages. Colocalization of the epitopes for oxidized LDL and apo B was not always observed, in contrast to the results reported by Haberland and co-workers.[70]

The immunostaining observed with antibodies to malondialdehyde- and 4-hydroxynonenal-modified LDL proteins cannot be viewed as conclusive evidence for the presence of oxidized LDL in the lesions, as these antibodies recognize only derivatized lysine residues and would bind to modified lysine residues in *any* protein (not just apo B). These studies also do not show that oxidation of the lipoproteins occurred before the lipoproteins were taken up by the macrophages. Studies by Mitchinson's group at Cambridge (England) University have shown that macrophages can oxidize lipids intracellularly and generate "ceroids" that are thought to be oxidized lipid-protein complexes.[71] Despite these qualifications, the immunohistochemical studies provide strong circumstantial evidence for LDL oxidation in the arterial wall. Another finding that lends circumstantial support to LDL oxidation in vivo is that in both rabbits and humans, autoantibodies frequently develop against oxidized LDL.[68]

Ylä-Herttuala and co-workers recently used immunohistochemical studies and in situ hybridization studies to compare the distribution of antibodies to oxidized LDL (such as malondialdehyde-derivatized proteins) and several gene products thought to be important in LDL oxidation and the generation of foam cells.[34,72] They demonstrated that the proteins containing epitopes of oxidized LDL colocalize with the messenger RNA for 15-

lipoxygenase in arterial lesions of WHHL rabbits.[72] As described earlier, 15-lipoxygenase is a cellular enzyme that may have a role in initiating LDL oxidation.[42] In a follow-up study, they examined human atherosclerotic lesions obtained from organ donors and found that the immunostaining of lesions with antibodies to oxidized LDL colocalized with the messenger RNA for 15-lipoxygenase and that for the acetyl-LDL receptor.[34] The immunohistochemical and in situ hybridization studies (together with the studies on LDL extracted from arterial lesions) favor the proposition that oxidized LDL exists in the arterial wall. These histologic studies, however, provide only "snapshots" of different events in the arterial wall and cannot by themselves be used to determine whether the observed phenomena are mechanistically related or whether they represent important events in atherosclerosis. Nevertheless, they lend support to the hypothesis of the existence of LDL oxidation in vivo and a possible role for the scavenger receptor-mediated uptake of cell-oxidized LDL in the generation of early atherosclerotic lesions.

Atherogenic Effects of Oxidized Low-Density Lipoprotein

As outlined, the internalization of oxidized LDL by scavenger receptors of arterial wall macrophages is a plausible mechanism for the formation of macrophage foam cells. Recent studies have indicated that oxidized LDL may be "double trouble" for macrophages. Not only is it taken up avidly by the scavenger receptor, but it also tends to accumulate within cells because of a defect in metabolizing oxidized LDL. Sparrow and colleagues showed that oxidized LDL accumulates within cells, in contrast to acetyl LDL.[73] Lougheed and associates recently demonstrated that the derivatization of apo B by lipid peroxidation products results in extremely inefficient digestion of the modified apo B by lysosomal proteases.[74] Inefficient degradation of oxidized LDL could be an important factor contributing to foam cell development because it could retard the efflux of ingested lipids. Furthermore, this finding could help to understand earlier reports[69] that oxidatively modified LDL can be demonstrated in macrophages by immunohistochemical techniques using various antibodies specific for derivatized lysine residues.

Aside from participating in foam cell development, oxidized LDL has many other properties that could play a role in atherosclerosis. One of the biologic effects of oxidized LDL is its cytotoxic effect on cultured endothelial cells. This effect was reported by Henriksen and colleagues and by Chisolm and co-workers.[37,75] Both groups observed that LDL that was incubated with cultured cells under conditions permitting oxidation became toxic to the cells. This work was extended by Chisolm and colleagues in recent years, and it now appears that the cytotoxicity of oxidized LDL is influenced by the phase of the cell cycle.[76] They have shown that cells in the proliferative phase are affected by oxidized LDL to a greater extent than are confluent, resting cells. Cytochalasin B, a blocker of cell proliferation and migration, as well as irradiation (which blocks cell proliferation), prevents the cytotoxic effects of oxidized LDL. Similarly, the treatment of cells with hydroxyurea to prevent them from entering the S phase of growth blocked the toxicity of oxidized LDL, indicating that cell toxicity is selective to cells in the S phase. Neither the active cytotoxin nor the precise mechanism(s) by which the toxicity of oxidized LDL is effected is clear at present. Antioxidants seem to ameliorate the cytotoxic effect of already oxidized LDL on cultured cells. For example, cells previously exposed to antioxidants appear to be protected against the cytotoxicity of oxidized LDL.[77] Whatever the exact mechanism, damage to the arterial endothelia by oxidized LDL could contribute to the development of atherosclerosis by increasing the flux of lipoproteins into the arterial intima, facilitating the entry of leukocytes into the intima, or by promoting thrombosis and platelet aggregation.

The effects of oxidized LDL may also explain why monocytes, the progenitor cells of tissue macrophages, enter the artery and why the macrophages become entrapped in the atherosclerotic artery. Quinn and associates have established that the lipid components of oxidized LDL contain chemotactic factors for circulating monocytes, possibly explaining the initial recruitment of monocytes into the arterial wall.[78] Furthermore, they have shown that the lipid components of oxidized LDL have the capacity to inhibit the migration of resident macrophages in culture, perhaps explaining why macrophages become trapped in the intima. Quinn and co-workers demonstrated that lysolecithin (generated by phospholipase A_2 during LDL oxidation) is responsible for the monocyte chemotactic activity of LDL.[79] These early studies were important because they stimulated enormous interest in elucidating new mechanisms (aside from foam cell formation) whereby oxidized LDL might contribute to atherogenesis. Other investigators have since established many other potentially proatherogenic properties of oxidized LDL (Table 2 and Figure 1). It is noteworthy that many of the effects of oxidized LDL are mediated by its lipid components.

Lysolecithin, a cytolytic lipid found in oxidized LDL, possesses several potent biologic properties. In addition to its monocyte chemotactic activity, it is chemotactic to T lymphocytes.[80] T lymphocytes, which are present in atherosclerotic lesions, together with monocytes-macrophages, produce various cytokines (such as interleukin-4 and gamma interferon) that have profound effects on monocyte-macrophage functions, including the induction and regulation of 15-lipoxygenase and the activity of the scavenger receptor. In contrast, B lymphocytes and neutrophils do not respond to chemotactic stimulus by lysolecithin. Lysolecithin also induces adhesion molecules on endothelial surfaces. Kume and colleagues reported that lysophosphatidylcholine induced the expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in cultured endothelial cells, a property mimicked by several other metabolizable lysophospholipids.[81] These adhesion molecules support the binding of

TABLE 2.—*Potentially Proatherogenic Effects of Oxidized Low-Density Lipoprotein (LDL)*

Biologic Effect	*Responsible Component of Oxidized LDL*
Increased uptake by macrophages	Modified protein
Monocyte chemotaxis	Lysophosphatidylcholine
Inhibited macrophage chemotaxis	Unknown lipid
Cellular cytotoxicity	Lipid, possibly an oxysterol
Inhibited endothelium-dependent relaxation	Lysophosphatidylcholine
T-lymphocyte chemotaxis	Lysophosphatidylcholine
Increased monocyte adhesion to endothelium	Unknown lipid
Induced granulocyte and macrophage colony-stimulating factors	Unknown lipid
Induced monocyte chemotactic protein	Unknown lipid
Increased interleukin-1 production	9-HODE, 13-HODE, modified protein
Increased antigenicity	Modified protein
Increased smooth muscle cell proliferation	Unknown components
Inhibited endothelial migration	Unknown lipid

9-HODE = 9-hydroxyoctadecadienoic acid, 13-HODE = 13-hydroxyoctadecadienoic acid

various leukocytes, including monocytes, to endothelial cells.

A potentially extremely important property of oxidized LDL is its ability to affect vasomotor properties of blood vessels. Many studies have documented pronounced vasomotor abnormalities accompanying atherosclerosis and hypercholesterolemia, including impaired responsiveness to vasodilators and augmented responses to vasoconstrictors.[82] Vascular endothelial cells synthesize endothelium-derived relaxing factor, which has properties similar (if not identical) to nitric oxide. This factor diffuses from endothelial cells and relaxes smooth muscle cells. Kugiyama and co-workers have shown that arteries exposed to oxidized LDL show an unresponsiveness to endothelium-derived vasodilators that is similar to that observed in atherosclerotic vessels.[83] They presented evidence that this defect was due to the lysolecithin in oxidized LDL. Chin and associates presented convincing evidence that a lipid component in oxidized LDL inactivates nitric oxide.[84] In addition to its effects on vascular tone, reducing levels of endothelium-derived relaxing factor may actually increase the development of atherosclerotic lesions in rabbits.[85] Oxidized LDL has also been reported to induce the expression of endothelin from human and porcine endothelium.[86] Endothelin is a polypeptide vasoconstrictor that could contribute to vasospastic events in atherosclerotic vascular disease.

The groups of Berliner and Fogelman at the University of California, Los Angeles, have extensively analyzed the biologic properties of minimally modified LDL.[61] These LDLs have only small amounts of oxidized lipids, little fragmentation of apo B, and insufficient apo B derivatization for recognition by the scavenger receptor; nevertheless, they may have extremely important proatherogenic properties. The treatment of cultured endothelial cells with minimally modified LDL causes a notable increase in the endothelial cell production of a chemotactic factor for monocytes and also results in an increase in the binding of monocytes to endothelial cells.[61] The activity responsible for these actions was located in the polar lipid fraction of the LDL. Subsequently, the same investigators have shown that the monocyte chemotactic factor produced by endothelial cells in response to minimally modified LDL is monocyte chemotactic protein 1.[87] They also showed that minimally modified LDLs cause a pronounced and rapid induction of various monocyte and granulocyte growth factors known to affect the migration, metabolism, survival, growth, and differentiation of monocytes-macrophages and endothelial cells.[88] Those growth factors could be important in the initiation and growth of early atherosclerotic lesions. The specific lipid components of oxidized LDL responsible for inducing monocyte chemotactic protein 1 and the monocyte-granulocyte growth factors are not yet known. In addition to these effects, minimally modified LDLs dramatically induce tissue factor production by endothelial cells.[89] This increased tissue factor production could be important in promoting thrombosis in atherosclerotic lesions.

Several other chemical components of oxidized LDL have been suggested to have potent biologic properties. For example, 9- and 13-hydroxyoctadecadienoic acid, oxidized fatty acid derivatives present in oxidized LDL, elicit interleukin-1 secretion from resting mouse peritoneal macrophages.[90] Interleukin-1 is a cytokine produced by monocytes-macrophages in response to various immune and inflammatory events. It can influence the pathogenesis of atherosclerosis by inducing vascular smooth muscle proliferation and promoting the adherence of

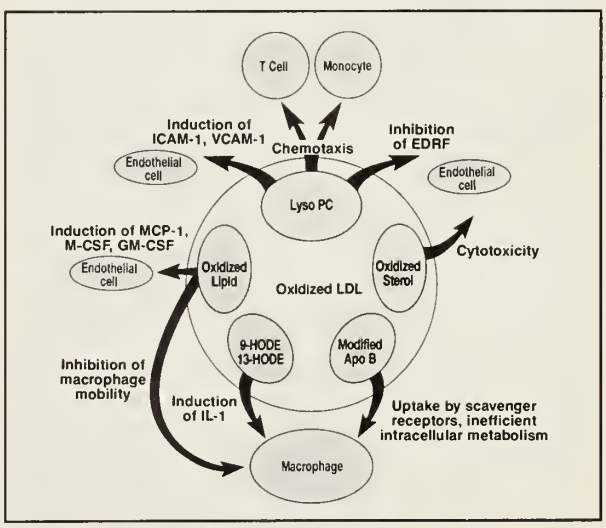

Figure 1.—Mechanisms are shown whereby various components of oxidized low-density lipoprotein (LDL) might contribute to atherogenesis. Apo B = apolipoprotein B, EDRF = endothelium-derived relaxing factor, GM-CSF = granulocyte and macrophage colony-stimulating factor, 9-HODE = 9-hydroxyoctadecadienoic acid, 13-HODE = 13-hydroxyoctadecadienoic acid, ICAM-1 = intercellular adhesion molecule-1, IL-1 = interleukin-1, Lyso PC = lysophosphatidylcholine, MCP-1 = monocyte chemotactic protein 1, M-CSF = monocyte colony-stimulating factor, VCAM-1 = vascular cell adhesion molecule-1

leukocytes to the endothelium. Recent results suggest that the protein component of oxidized LDL can induce the release of interleukin-1 from foam cells isolated from the atherosclerotic lesions of cholesterol-fed rabbits (B. A. Lipton, S. Parthasarathy, V. A. Ord, S. K. Clinton, P. Libby, M. E. Rosenfeld, "Oxidized Low-Density Lipoprotein Stimulates Interleukin-1 Production by Rabbit Arterial Foam Cells," April 1993, unpublished manuscript). Acetyl LDL does not share this property.

In addition to those effects, oxidized LDL has several other proatherogenic effects. For example, recent studies of Murugesan and colleagues show that oxidized LDL, presumably a lipid peroxide, inhibits the migration of endothelial cells.[91] These authors point out that such an effect, if it persists in vivo, could compromise the response of the endothelium to wound healing after injury.

The effects of oxidized LDL on gene expression and on cellular metabolism are being studied intently in many laboratories, and new reports appear monthly. Despite the excitement generated by this research, caution should be exercised in interpreting the reported biologic effects of oxidized LDL, because many of the in vitro cell culture experiments may not accurately reflect in vivo conditions in the arterial wall. We also emphasize that some effects of oxidized LDL may not be atherogenic. For example, it has been suggested that oxidized LDL increases prostacyclin production by cultured cells.[92] It also suppresses the synthesis of platelet-derived growth factor-β[93] and tumor necrosis factor-α synthesis[94] by endothelial cells and macrophages. Whether these phenomena are atherogenic is not yet clear.

Evidence That Oxidized Low-Density Lipoproteins Are Important in Atherogenesis

As outlined, immunohistochemical studies and in situ hybridization studies on the arterial wall provide strong evidence that oxidized LDL exists within atherosclerotic lesions, and many different biologic effects of oxidized LDL are potentially atherogenic. But how important are these observations? Is oxidized LDL simply an innocent bystander, or does it play a key role in the pathogenesis of atherosclerosis? The most striking evidence in favor of the importance of oxidized LDL in atherogenesis comes from studies of animals indicating that administering antioxidants can retard the development of atherosclerosis. Several of the most convincing studies on these antiatherogenic properties were performed with the hypolipidemic agent probucol. In humans, probucol lowers LDL-cholesterol levels only slightly, but it usually lowers HDL levels substantially. Probucol is lipophilic and is carried in the plasma almost exclusively by lipoproteins. It is also a powerful antioxidant—even more powerful than vitamin E. Low-density lipoprotein prepared from the plasma of human subjects taking therapeutic doses of probucol is highly resistant to oxidative modification by cultured endothelial cells when compared with control LDL preparations and consequently has considerably reduced uptake by cultured macrophages.[95] Carew and coworkers tested whether probucol would reduce atherosclerosis in WHHL rabbits.[96] Their study included a group of probucol-treated animals and two control groups. One control group was given no drug and the other control group was given small doses of lovastatin titrated carefully to maintain cholesterol levels at the same level as those in the probucol-treated animals. After seven months, they observed an approximately 50% reduction in the surface area of lesions in the probucol-treated animals compared with those of the cholesterol-matched, lovastatin-treated controls. Furthermore, using sophisticated arterial wall metabolism studies that involved radiolabeled LDL tracers, they documented that in the probucol-treated group, the uptake and degradation of LDL within the lesioned areas of the aorta were reduced compared with those in the lovastatin-treated group. Virtually simultaneously, Kita and colleagues performed similar studies on the effect of probucol on atherosclerosis in WHHL rabbits, and they found essentially identical results—a major reduction in atherosclerotic lesions.[97] Since these two studies, the antiatherogenic properties of probucol have been established by various laboratories both in WHHL rabbits and in cholesterol-fed rabbits.[98]

The efficacy of antioxidants in cholesterol-fed animals, particularly in rabbits, in which the predominant cholesterol-carrying lipoprotein is β-VLDL, raises an interesting issue. The β-VLDLs are large, cholesterol-rich lipoproteins that contain a substantial amount of apo E in addition to apo B. These lipoproteins are taken up effectively by macrophages by an apo E-mediated pathway, a situation that can lead to massive cholesterol accumulation without any requirement for oxidative modification. The effectiveness of antioxidants in retarding atherosclerosis in cholesterol-fed rabbits suggests the possibility that the oxidation of β-VLDL plays a role in inducing atherosclerosis in this experimental model. In vitro studies suggest that β-VLDLs undergo oxidative modification similar to that observed with LDL and that the modified β-VLDLs are taken up by macrophages by the scavenger receptor. Oxidation of β-VLDL in vivo offers a possible explanation for a portion of the foam cell formation and for some of the other pathologic features of atherosclerosis (such as the attraction of T lymphocytes and macrophages into the lesions).

In addition to its antioxidant properties, probucol also affects LDL- and HDL-cholesterol levels, inhibits the release of interleukin 1 from macrophages, and increases the transfer of cholesteryl esters from HDL to LDL. Consequently, the antiatherogenic properties of probucol may not be due solely to its antioxidant properties. To examine this issue further, scientists at Marion Merrell Dow Inc (Kansas City, Missouri) have developed and characterized several chemical derivatives of probucol that retain antioxidant and lipophilic properties but have minimal or no effects on lipoprotein metabolism.[99,100] These analogues retained the ability to inhibit atherosclerosis in WHHL rabbits, implying that the antioxidant properties of probucol may play a key role in inhibiting atherogenesis. The notion that probucol's antioxidant effects are important

is supported by the fact that other antioxidants, including butylated hydroxytoluene[101] and *N,N'*-diphenyl-1,4-phenylenediamene,[102] have antiatherosclerotic effects in animal models. Sparrow and associates showed that *N,N'*-diphenyl-1,4-phenylenediamene effectively inhibited LDL oxidation in vitro at low concentrations and found that it reduced the incidence of aortic lesions in cholesterol-fed rabbits by 50% to 70% without affecting total plasma cholesterol levels.[102]

Another major reason to think that oxidized LDL may be important in atherogenesis is that epidemiologic studies have indicated that plasma levels of natural antioxidants are inversely proportional to the risk of ischemic heart disease. Gey and co-workers ascertained levels of vitamin E and other plasma antioxidants in 16 different European populations that differed sixfold in mortality from ischemic heart disease.[103] Among 12 populations with similar cholesterol levels (clustered around "normal" levels—5.70 to 6.20 mmol per liter [220 to 240 mg per dl]), the blood pressure readings and the serum cholesterol levels were not predictive of ischemic heart disease mortality. A striking inverse correlation was found, however, between heart disease mortality and vitamin E levels. Inverse relationships also were observed between heart disease risk and two other antioxidants, vitamins A and C, although the relationships were considerably weaker. The inverse relationship of ischemic heart disease risk and antioxidants remained significant after adjustment for other classical risk factors—smoking, blood pressure, and cholesterol level.

Stampfer and colleagues recently reported on a prospective study of the relationship between antioxidant vitamin intake and ischemic heart disease in more than 87,000 female nurses.[104] They found a significant (~35%) reduction in coronary heart disease risk in women with the highest quintile of vitamin use versus women with the lowest quintile of vitamin use, and this finding remained significant after adjustment for age, smoking, and other heart disease risk factors. The apparent benefit of vitamin E was largely confined to those who consumed vitamin E supplements for more than two years. Similarly, Rimm and associates assessed vitamin intake in more than 39,000 healthy male health care professionals.[105] During four years of follow-up, 667 cases of coronary artery disease occurred. For men consuming more than 60 IU per day of vitamin E, the risk of coronary disease was reduced by approximately 35%. No decrease in coronary risk was noted in men who had reported a high intake of vitamin C. Riemersma and co-workers reported on a case-control study that supported an inverse relationship between the plasma vitamin E level and the incidence of angina pectoris.[106] In this study, they measured vitamin E levels of 110 patients with angina and 394 control subjects. Patients with angina had significantly lower vitamin E levels, even after adjustment for smoking habits, age, lipid levels, weight, and blood pressure.

No large, prospective, randomized trials have tested whether administering antioxidant vitamins would reduce the incidence of atherosclerosis in humans. The best prospective evidence to date comes from a preliminary report from the Harvard Physicians Health Study that was originally designed to test the hypothesis that β-carotene might reduce cancer rates.[107] This study enrolled 333 male physicians with angina pectoris, coronary revascularization, or both. Those men assigned to receive β-carotene, 50 mg on alternate days, had a 44% reduction in major coronary events ($P < .05$) and a 49% reduction in all major vascular events ($P < .02$) after adjustment for age. Controlling for aspirin use and other major risk factors did not affect these findings. This randomized trial is continuing, and data on the primary prevention of heart disease with β-carotene should become available in a few years. Another large-scale trial testing vitamin E and β-carotene use in the primary prevention of heart disease has recently been funded by the National Institutes of Health.[107]

Several other intriguing studies in humans provide suggestive evidence for the importance of oxidation in atherogenesis. Salonen and associates analyzed whether the titer of antibodies directed against epitopes in oxidized LDL have any predictive value in the progression of carotid atherosclerosis in Finnish men.[108] They compared antibody titers against malondialdehyde-modified LDL in 30 men with accelerated progression of carotid atherosclerosis and in 30 controls without progression. Those with accelerated progression had a significantly higher antibody titer than controls, and the titer of antibodies remained significant in a multifactorial logistic model that considered many other atherosclerotic risk factors. This preliminary study suggests that the titer of antibodies against oxidized LDL might be correlated with the activity of the atherosclerotic disease process. These findings need confirmation, especially because the same investigators did not find any difference between cases and controls with respect to titers of other oxidized LDL autoantibodies.[108] If the results of these immunochemical studies are borne out by future studies, they will suggest that an immune response triggered by oxidized LDL may be important in atherogenesis.

Another recently published chemical study lending support to the pathogenetic importance of oxidized LDL analyzed the length of "lag phase" preceding copper ion-induced LDL oxidation in a group of patients who had had myocardial infarction and had undergone coronary angiography.[58] The authors found an inverse relationship between the lag phase and quantitative estimates of global coronary atherosclerosis, supporting the notion that the quantity of natural antioxidants in LDL has a clinically important effect on atherosclerosis.

Where We Stand With Oxidized Low-Density Lipoprotein

Considerable evidence has now accumulated that the oxidation of LDL in vivo plays an important role in atherogenesis. The story began with cell culture observations indicating that the oxidation of LDL could promote its uptake by macrophages and was toxic to endothelial cells. But in recent years, laboratory studies have focused

on several new mechanisms whereby LDL oxidation, even to minimal degrees, might be atherogenic. Studies of humans and animals have demonstrated the existence of oxidized LDL in atherosclerotic lesions. Studies of animals showing the antiatherogenic effects of several different antioxidants have strongly suggested that the oxidation of LDL plays a key role in atherogenesis. Epidemiologic studies showing an inverse relationship between antioxidant vitamin levels and heart disease have also lent credence to the hypothesis that oxidized LDL is important in atherogenesis.

The emergence of oxidized LDL as a potentially important "player" in atherosclerosis is exciting for both basic scientists and clinicians. For basic scientists, the oxidized LDL explanation has begun to shed light on the "black box" between high levels of LDL in the blood and the development of atheromas in the artery wall. Illuminating the pathway between high cholesterol levels and atherosclerosis has posed many new questions for investigators of atherosclerosis. For example, the topic of precisely which cellular chemical reactions are responsible for the initiation of LDL oxidation in the arterial wall is currently an active area of research. Further research into the mechanism of LDL oxidation may uncover new targets for the drug treatment of atherosclerosis. If 15-lipoxygenase turns out to be the most important enzyme in the initiation of LDL oxidation in the arterial wall, then searches for potent and safe 15-lipoxygenase inhibitors would be in order.[38] Similarly, which natural antioxidants are most effective is a hot topic of research. If future research indicates that ubiquinol-10 is the most effective natural antioxidant, as some have suggested,[109] then intervention studies with this agent should be done. The possible importance of oxidized LDL has led many scientists to focus their efforts on understanding the biology of specific gene products, such as the acetyl-LDL receptor and 15-lipoxygenase.[38] Over the next three or four years, new animal models will likely be created that lack these gene products or overexpress the gene products in the arterial wall. Study of these animals will undoubtedly help to clarify the importance of these gene products in the generation of oxidized LDL and macrophage foam cells.

From the point of view of clinicians, the recent studies on oxidized LDL hold out the promise of a relatively quick payoff. It has been less than a decade since oxidized LDL was proposed as having a possible role in atherosclerosis, yet primary prevention trials are already underway, and angiographic trials to assess the effect of natural antioxidants on coronary anatomy will begin soon.[107] If natural antioxidants are effective in humans, a new approach to the treatment of heart disease will have been established, and physicians would then have to be concerned with the concentration of LDL in their patients' plasma as well as protecting their patients' LDL from oxidation within the artery wall.

Oxidized LDLs have recently gained a lot of attention in the lay literature, and a large percentage of the United States population now consumes antioxidant vitamins with the hope of preventing heart disease. Should physicians "jump the gun" on the scientific trials and begin to recommend antioxidant vitamins or drugs to their patients? Steinberg has recently argued articulately and persuasively that we should await large, prospective, long-term, double-blind clinical trials in humans before advocating vitamin E supplements to our patients.[110] We agree with this point of view. Although the oxidized LDL hypothesis is tantalizing, we should insist on solid clinical trial evidence before making public health policy.

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Epitomes

Important Advances in Clinical Medicine

Urology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in urology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Management of Benign Prostatic Hyperplasia

SURGICAL THERAPY FOR benign prostatic hyperplasia has typically been done through either open enucleation or transurethral resection or incision of the prostate. The choice between the various procedures is usually based on the size and configuration of the prostate. In the United States, 90% of prostatectomies are done transurethrally, and about 400,000 transurethral resections were done in 1992. The procedure is considered relatively free of life-threatening complications, and in most patients (80%), relief of obstructive symptoms is achieved. This procedure requires anesthesia and usually a three-day hospital stay; important problems such as bleeding can occur. Alternative forms of interventional therapy are being investigated, with the goals to maintain the efficiency of transurethral surgery as a one-time treatment while lowering the invasiveness and the cost.

Interventional treatment alternatives include balloon dilation, prostatic stents, microwave heating, and laser ablation. Balloon dilation of the prostate came into vogue five or six years ago. With this technique, a balloon catheter is passed through the urethra and the balloon inflated to at least 30 mm of mercury and 90-F catheter size in the prostatic fossa. The procedure is usually done under regional anesthesia, often as an outpatient procedure. An indwelling catheter is often left in for 24 to 48 hours. The technique gives reasonable short-term relief in selected patients, but long-term studies show diminishing effectiveness after 12 to 24 months. Prostatic stents are spiral springs made of stainless steel or titanium that are placed under anesthesia in the prostatic fossa and the prostatic urethra expanded to a diameter as large as a 42-F catheter. Patients can typically be discharged the day of the procedure or the next morning without a catheter. The most common complaint afterwards has been a feeling of irritation by the presence of the stent. Urethral damage and proximal migration or epithelialization may occur in 20% to 30% of patients, and the stent may need to be removed. Prostatic stents are not currently approved by the Food and Drug Administration (FDA), but have been used in Europe for the past few years.

Microwave heating of the prostate has been explored in this country since 1986. A catheter is placed transurethrally into the prostatic fossa, and microwave antennae are used to heat the surrounding prostate tissue to a minimum of 45°C without anesthesia. Heating causes fibrosis and retraction of the surrounding tissue. This can be done in the office as an outpatient procedure. The technique, although widely used in Europe and Canada, is available in the United States only at selected centers and has not been approved by the FDA. Results are comparable or superior to those of medical agents, but are less than those of transurethral prostatic resection; they have held up over the seven years that this therapy has been studied.

Three types of laser techniques have been used to treat benign prostatic hyperplasia. Prostatic tissue is visualized endoscopically or by ultrasound imaging. All use the neodymium:yttrium-aluminum-garnet wavelength as an energy source. The principal differences have been in the method of energy delivery and technique of therapy. The most common type of delivery system uses a metal-tip reflector to reflect laser energy into the prostate. In this technique the prostate is coagulated at 40 to 60 W laser power for 60 to 90 seconds in a noncontact mode to the four quadrants of the prostate. The technique produces

coagulative necrosis of the adenoma and tissue absorption, which occurs over a few weeks to a few months. The disadvantage of the technique is that metal-tip reflector fibers cannot be used in a contact mode because tissue will adhere to the metal reflector, causing excessive heat buildup and damage to the fiber. The second technique involves a sapphire-tip contact laser fiber that relies on the laser energy to heat the tip, which is then used to coagulate and evaporate the tissue. The tip, being small, can make contact with only a certain amount of tissue. This technique is time-consuming and therefore more useful for prostatic incision than for evaporation. A third technique uses a free beam, quartz-tip fiber in a contact mode to enhance evaporation. Fibers using quartz-tip reflectors are amenable to contact evaporation because quartz has a melting point close to 900°C.

All three techniques in preliminary follow-up studies show improvements in symptom scores and urinary flow that are comparable to conventional transurethral resection. The principal advantages of laser ablation include the lack of bleeding (it can be done on patients taking warfarin sodium), a lack of fluid absorption (it can be done on high-risk patients), and its ambulatory nature (it saves hospital costs). Because no tissue is removed for histologic examination, incidental or stage A cancer of the prostate cannot be detected. Current instruments and techniques are still evolving. Safety and long-term efficacy are still unknown.

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Vasectomy and Prostate Cancer

CONCERNS HAVE BEEN RAISED recently about a possible increased incidence of prostate cancer in men who have had a vasectomy. A retrospective study of 14,607 husbands of nurses and 14,607 age-matched controls revealed that the relative risk of prostate cancer developing in men who had undergone a vasectomy was 1.56 (95% confidence interval [CI] 1.03 to 2.37; $P = .04$). A second prospective study evaluated 10,055 male health care professionals who had had a vasectomy and 37,800 who had not. The relative risk of prostate cancer developing in the men who had had a vasectomy was 1.61 (CI 1.25 to 2.21; $P < .01$). Because 50 to 60 million men worldwide have had a vasectomy and prostate cancer occurs in 1 of 11 American men, any real association between vasectomy and prostate cancer would be of great concern. Although these studies were well-done epidemiologic investigations, the association is weak (although statistically significant) and is not convincing. This weak association could be due to chance or to bias. The most likely would be a selection bias because men who have undergone a vasectomy, particularly in the era when these particular men had their vasectomies, may be more likely to seek sophisticated medical care, be evaluated by a urologist, and have an early diagnosis of prostate cancer. Thus, unmeasured confounding could explain this weak association.

The possible relationship between vasectomy and prostate cancer has to be viewed with some skepticism because two other studies, one of which had long-term follow-up, did not find any effect. In addition, there is no biologically plausible explanation for a relationship between a vasectomy and prostate cancer. In view of the weak epidemiologic association, the lack of consistency with other cohort studies, and the absence of a logical biologic mechanism, the data are too preliminary to suggest any change in the current policy regarding vasectomy.

Epidemiologic studies (as yet unpublished) have shown no evidence of a link between prostate cancer and vasectomy. In a follow-up of a previously published study, a relative risk of 1.1 (CI 0.5 to 2.4) was documented; 15 years after the vasectomy, the relative risk was 0.8. In a case-control study with 1,000 cases diagnosed between 1986 and 1989 and 1,300 controls, the relative risk was 1.2 (CI 0.8 to 1.7). There was no increased risk with time after the vasectomy or with increased age at the time of vasectomy. A third study examined 2,351 men who had had a vasectomy and an equal number of controls. A total of 127 cases of prostate cancer were found in the men with a vasectomy and the controls more than 20 years after the procedure, compared with only 53 cases of prostate cancer more than 20 years after a vasectomy in other studies. The relative risk was 1.1 (CI 0.8 to 1.3) with no increased relative risk at 20 or 30 years after vasectomy.

Results were recently reported of digital rectal examinations and prostate-specific antigen (PSA) tests done on 35,000 men, 8,000 of whom had had a vasectomy, during Prostate Cancer Awareness Week. There was no difference between the frequency of abnormalities found on digital rectal examination or positive PSA tests for any age group between men with and those without a vasectomy. In view of the new data and the problems with the original studies, vasectomy should continue to be offered as a form of male sterilization as long as patients requesting it are informed of the published studies and make their own decision. An actual association between vasectomy and prostate cancer is unlikely. Men who have had a vasectomy should be screened annually with a digital rectal examination and PSA test after the age of 50. This is the same recommendation that the American Urologic Association and the National Cancer Association have made for all men.

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Howards SS, Peterson HB: Vasectomy and prostate cancer: Chance, bias, or a causal relationship? JAMA 1993; 269:913-914

Imaging of Pediatric Testicular Problems

THE MOST COMMON of the testicular problems for which imaging is recommended is cryptorchidism. Undescended testes can be identified noninvasively with ultrasonography, computed tomography, and magnetic resonance imaging. These modalities work best when the testis is in the groin and are least sensitive for intra-abdominal testes. Hence, testes that are palpable on a careful physical examination are most likely to be identified by imaging; those that are not palpable are most likely to be missed. Therefore, imaging for undescended testes is not clinically helpful and, in this era of limited resources, is not cost-effective.

Boys presenting with an acutely inflamed scrotum are another group for whom imaging is used to establish the diagnosis of testicular torsion. Radionuclide testicular scanning (often with pin-hole collimation) has proved reliable in detecting testicular blood flow. Color-flow Doppler studies have been used in adults and seem accurate, but thus far their reliability in prepubertal children has as yet not been established. The major drawback to any imaging study in acute scrotal inflammation is the time required to do the study. Because successful salvage of a testis in patients with testicular torsion inversely depends on the length of the time the testis has been ischemic, only if studies can be obtained within 30 to 60 minutes is their use appropriate, and then only to refute the diagnosis of torsion of the testis. If torsion of the testis is a serious consideration in the differential diagnosis, it is often best to omit confirmatory imaging studies and to proceed directly and expeditiously to surgical exploration.

Testicular tumors can be imaged with ultrasonography. The identification of a cystic lesion in the testis may result in enucleation of the lesion rather than orchiectomy. A solid lesion within or replacing the testis most likely is a tumor, and radical orchiectomy can be performed with confidence. Cystic lesions in a prepubertal testis most often represent a teratoma or epidermoid cyst, both of which are uniformly benign before puberty and therefore lend themselves to a testis-sparing procedure.

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Urologic Laparoscopic Procedures

MANY UROLOGIC APPLICATIONS OF laparoscopic surgery have been developed over the past several years. In particular, laparoscopic lymph node dissections for prostate cancer staging and laparoscopic varicocele ligation have been used extensively. As urologists' skill levels and instruments improve, these procedures will be further refined and new procedures developed. In turn, minimally invasive laparoscopic procedures can be compared to standard open surgical procedures with respect to efficacy and morbidity.

In patients with prostate cancer, the state of the obturator lymph nodes provides important prognostic information. Obturator lymphadenectomy, when done laparoscopically, is associated with minimal morbidity, and the yield in the lymph node harvest is comparable to an open transabdominal procedure. In patients undergoing radical prostatectomy, many urologists are now using the perineal approach after a staging laparoscopic lymphadenectomy, so patients can avoid any major abdominal incisions.

Laparoscopic varicocele ligation appears to be as efficacious as the open approach. The morbidity is similar and also minimal, but the procedure may be more advantageous in bilateral cases. In children with undescended testes, laparoscopy can be both diagnostic and therapeutic. Intersex problems can also be treated laparoscopically, for example, in gonadectomy. Female patients with stress urinary incontinence have been treated with standard open repairs (Marshall-Marchetti-Krantz or Burch) or a minimally invasive approach (Stamey or Raz procedure). The laparoscopic approach to the former procedures combines the anatomical soundness of these repairs with their minimal morbidity.

As more laparoscopic experience is gained, more complex procedures have been attempted. The results of nephrectomy, pyeloplasty, partial nephrectomy, renal cyst excision, and adrenalectomy have all been reported in initial series. Whereas the first attempt at these procedures has been associated with prolonged operative times, the experience with most investigators is rapidly increasing. Ureterolysis, ureterolithotomy, and other retroperitoneal procedures, such as lymphadenectomy for clinical stage A testis tumor, have been done.

For these newer, albeit investigational, laparoscopic procedures to become standard, they must not only be associated with equivalent or improved morbidity and efficacy, but also be cost-effective. Initial prolonged operative times and the high use of expensive disposables must be offset by the advantages of the newer procedure.

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Prostate-Specific Antigen in Screening for Prostate Cancer

PROSTATE-SPECIFIC ANTIGEN (PSA) is a serine protease produced by prostatic epithelial cells, with minute quantities "leaking" into the serum. The serum level of PSA is frequently elevated in disease states of the prostate such as infarction, inflammation, benign prostatic hyperplasia, and carcinoma. Although routine digital rectal examination of the prostate gland does not substantially elevate serum PSA levels, other forms of prostatic manipulation—urethral catheterization, prostatic massage, cystoscopy, prostatic biopsy, or transurethral resection of the prostate—will. Recent studies have shown that screening serum PSA determinations usually detect clinically significant prostate cancer before any signs of the disease appear and are more reliable than digital rectal examination when either method is used alone. Digital rectal examination should not be omitted because as many as 20% of men treated for curable prostate cancer with cancer that is digitally palpable have a PSA level in the normal range.

In 1993 the American Cancer Society recommended that men between the ages of 50 and 70 with a ten-year life expectancy should undergo annual digital rectal examinations and serum PSA tests for screening for prostate cancer. Because of the higher incidence of presumably more aggressive prostate cancer in African Americans, it has been proposed that annual screening in this group begin at age 40. Recent evidence supports the recommendation that men with a family history of prostate cancer be seen at an earlier age than men with no hereditary history, with screening also starting at age 40.

Any patient with a palpable, firm nodule on the prostate that suggests prostate cancer should be considered for a biopsy, irrespective of the PSA value. Likewise, any patient with a PSA level above 10.0 μg per liter should also be strongly considered for biopsy because as much as 70% of the time they will have a biopsy specimen revealing carcinoma. In patients with a serum PSA level between 4.0 and 10.0 μg per liter without a suspicious nodule on digital rectal examination, transrectal ultrasonogram-guided biopsy may be done or the patient may be actively observed with a repeat digital rectal examination and a PSA test in six months. The prostate cancer detection rate in these patients is about 25%, with most patients showing benign prostatic hypertrophy on biopsy. Nevertheless, a serum PSA elevation of 0.75 μg per liter in one year is worrisome for carcinoma and warrants a biopsy being done.

Screening for prostate cancer with digital rectal examination and PSA tests detects cancer in its earlier stages. In the recent Prostate Cancer Awareness Week screening efforts, about 3% of the patients with cancer detected had disseminated disease at the time of diagnosis. Prostate cancers that are detected only by slight PSA elevations are often of large volume and high grade, indicating that routine screening with PSA tests does not detect a high proportion of "latent," "clinically insignificant," "autopsy" carcinomas. It is recognized that prostate tumors usually grow slowly; strong consideration should therefore be given to any underlying medical conditions that might decrease the life expectancy of a patient and negate any possible benefit of therapy. Although early prostate cancer is detected using these combined methods, the question of "lead-time bias" has been raised regarding the effectiveness of early cancer detection programs. Longitudinal studies of the effectiveness of PSA screening programs are in progress.

Finally, although it is estimated that it costs $2,000 to detect one case of prostate cancer through mass screening efforts, this cost compares favorably with the estimated $12,000 to $14,000 per case of breast cancer detected in mass screening trials. Clearly, intelligently designed mass-screening protocols for the early detection of prostate cancer, using digital rectal examination and PSA levels, is a simple, cost-effective method of detecting clinically significant prostate cancers in their earlier stages.

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Treating Impotence

IN A RECENT SURVEY OF urologists, 85% reported treating patients with impotence with penile pharmacologic injections, vacuum erection devices, or surgically implanted prostheses. The practice of empirically giving testosterone injections has given way to a more advanced approach to diagnosis and treatment. Evaluation includes a history, physical examination, and elective endocrine studies including serum testosterone, prolactin, or luteinizing hormone levels. Office evaluation usually includes the intracavernous administration of one or a combination of vasoactive agents: prostaglandin E, papaverine hydrochloride, or phentolamine. Observing the erectile response, rigidity, penile curvature, and the rapidity of detumescence provides further information by which a patient's condition can be categorized as vascular (arterial insufficiency or venous leakage), neurogenic, endocrine, traumatic, or psychogenic. It is estimated that in more than 80% of impotent patients, the problem is organic in origin. Further testing may include nocturnal penile tumescence monitoring, duplex Doppler ultrasonography of the cavernosal arteries, dynamic infusion cavernosometry and cavernosography, and angiography. Use of these tests should be selective and tailored to a patient's treatment goals.

Although it has long been known that erections are primarily a hemodynamic event mediated through the autonomic nervous system, recent findings have shown the importance of penile smooth muscle relaxation for tumescence. A multitude of hormones, neurotransmitters, and neuromodulators in the penis are involved in corporal relaxation: acetylcholine, vasointestinal peptide, prostaglandin, and endothelium-derived substances. Of primary importance is the release of nitric oxide from endothelial cells that diffuses into adjacent smooth muscle cells, causing relaxation. Following filling of the endothelial lined lacunar spaces of the penis with blood, tumescence occurs and progresses to rigid erection when the veno-occlusive mechanism traps blood. Dysfunction of the veno-occlusive system seems to result from defects in the penis rather than the veins themselves.

For venous leakage, pelvic embolization of the veins and surgical resection of penile veins have shown a 40% to 50% initial success rate with a disappointing long-term success rate of only 15%. A new implantable, inflatable, cavernous compression device may improve treatment results. In patients with pure arterial insufficiency without corporal veno-occlusive dysfunction, limited experience with revascularization by an inferior epigastric artery bypass has shown a durable improvement in 50% to 75% of selected patients with a five-year follow-up.

Medical therapy with oral yohimbine hydrochloride or trazodone hydrochloride is effective in 20% of patients, but the contribution of a placebo effect is unknown. Vacuum constriction or negative pressure devices are gaining some patient acceptance, probably because of the less invasive nature. The penis is placed in a cylinder where negative pressure is applied. After adequate rigidity is achieved, an elastic constrictive device is placed at the base of the penis to prevent blood leaking back to the systemic circulation. Implanting a penile prosthesis remains an effective therapy. Improvements in design have led to semirigid, positionable, and inflatable designs with low mechanical failure rates. In 20 years, surgically implanted silicone penile prostheses have not been implicated in noninfectious systemic or immunologic complications.

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Complete Androgen Blockade for Metastatic Prostate Cancer

THE IDEAL FORM OF hormonal therapy in advanced prostate cancer remains to be determined. Much controversy exists regarding complete versus incomplete androgen blockade. Testicular androgen deprivation may be accomplished by orchiectomy or a luteinizing hormone-releasing hormone agonist such as leuprolide or goserelin. The addition of an androgen-receptor antagonist such as flutamide or nilutamide results in complete androgen blockade. Several clinical studies have reported objective responses to flutamide or aminoglutethimide in patients whose disease had progressed following orchiectomy. These observations have prompted several randomized clinical trials to study complete versus incomplete androgen blockade.

In the largest series to date, 603 patients with stage D2 prostate cancer were randomly assigned to receive leuprolide alone versus leuprolide and flutamide. Statistically significant pain abatement and increases in median progression-free survival (16.9 versus 13.8 months) and overall survival (35.6 versus 28.3 months) occurred in the patients with complete androgen blockade. The extent of disease was found to be an independent prognostic variable. A subset of 81 patients with minimal disease (axial skeleton metastases only) had more impressive differences in both the median progression-free survival (58.3 versus 19.1 months) and overall survival (61 versus 41.5 months), with the results favoring the patients with complete androgen blockade.

In another study, 307 patients were randomly assigned to receive goserelin and flutamide versus orchiectomy alone. Significant increases in pain abatement, median progression-free survival (16.4 versus 10.6 months), and cancer-related survival (48 versus 33 months) were seen in the patients with complete androgen blockade.

In a third study, 194 patients were randomly selected for orchiectomy and nilutamide or orchiectomy alone. Again, significantly decreased pain and increases in the percentage of favorable responses were seen in the patients with complete androgen blockade. Overall survival was greater in those having blockade, but it did not reach statistical significance (24.3 versus 18.9 months). Similarly, in a multinational study 423 patients were randomly assigned to treatment with orchiectomy and nilutamide or orchiectomy alone. Significantly decreased pain and increases in the percentage of favorable responses, median progression-free survival (20.8 versus 14.9 months), and cancer-related survival (37.0 versus 30.0 months) were seen in the patients with complete androgen blockade.

The cost of androgen deprivation therapy varies according to the method used. Orchiectomy may be the most cost-effective method of testicular androgen ablation, yet may be associated with psychological sequelae. Luteinizing hormone-releasing hormone agonist therapy requires monthly injections that may cost about $400 each. Impotence and hot flashes are common side effects of testicular androgen ablation. Androgen-receptor antagonists cost about $250 per month, and their use may be associated with gynecomastia and gastrointestinal side effects.

Current randomized trials suggest a statistically significant benefit to complete androgen blockade in patients with metastatic prostate cancer. Although the overall survival benefit may be modest (7 months), other measures such as quality of life, pain abatement, and percentage of responders are more substantial. Early data in patients

with low-volume disease are encouraging and warrant further investigation.

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Alerts, Notices, and Case Reports

Reactive Arthritis Induced by *Clostridium difficile*

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REACTIVE ARTHRITIS without microbial invasion of the joint is associated with various viral, bacterial, parasitic, and mycoplasmal infections. I report an unusual case of reactive arthritis associated with *Clostridium difficile*-induced pseudomembranous enterocolitis.

Report of a Case

The patient, a 66-year-old man with excellent health in the past, was well until three weeks before hospital admission when an abscess developed in a tooth. He was treated with oral penicillin VK, 250 mg four times a day. On the third day of penicillin treatment, intermittent, diffuse, crampy abdominal pain developed. The next day profuse, watery, nonbloody diarrhea accompanied his abdominal pain, occurring 10 to 15 times per day. Over the next ten days the patient's abdominal pain and diarrhea lessened but did not disappear, occurring once or twice a day. Seven days before admission and ten days after the onset of diarrhea, he awakened with a swollen, painful right fourth toe. The following day he had increased pain and swelling in his right knee and right shoulder. The pain progressively worsened and was unrelieved by aspirin. He then sought medical attention, was found to have a fever of 38.9°C (102°F), and was admitted to the hospital.

There was no history of similar episodes of arthritis and diarrhea, foreign travel, shellfish ingestion, chills, skin rash, sore throat, dysuria, urethral discharge, conjunctivitis, uveitis, or photophobia. His daughter had had idiopathic uveitis several years previously.

On physical examination he was alert, thin, and appeared sick, with a pulse rate of 100 beats per minute, a blood pressure of 120/70 mm of mercury, and a temperature of 38.9°C. The right knee, right shoulder, and the proximal interphalangeal joint of the right fourth toe were swollen, with increased warmth, tenderness, and erythema. There were no petechiae, splinter hemorrhages, or rash. The other physical findings were normal, with the exception of deafness and a slightly enlarged prostate.

Synovial fluid from aspiration of the right knee effusion revealed a leukocyte count of 30×10^9 per liter (30×10^3 per mm^3), with 0.60 neutrophils and 0.40 lymphocytes; no crystals; a negative Gram's stain; and no growth on culture. Sigmoidoscopy revealed classic pseudomembranous colitis. Culture of stool specimens was negative for *Yersinia, Salmonella, Shigella,* and *Campylobacter* species. Stool culture grew *C difficile,* but no toxin was identified. Stool examinations did not reveal ova or parasites. Tests for antinuclear antibody, rheumatoid factor, occult blood in the stool, and cultures of blood were negative; the complete blood count, chemistry values, chest film, and electrocardiogram were normal. X-ray films of the right shoulder and right knee were normal with the exception of effusions.

The patient was initially treated with ibuprofen, 600 mg four times a day, and vancomycin hydrochloride, 500 mg orally every six hours. His symptoms disappeared entirely within 48 hours. Therapy was then switched to oral metronidazole, 250 mg three times a day, and he completed an eight-day course of oral antibiotics. He had complete resolution of all joint symptoms and signs at the completion of antibiotic therapy and discontinued taking ibuprofen.

Seven days after completing the course of antibiotics, he again had the onset of diffuse, crampy abdominal pain and profuse, nonbloody, watery diarrhea. Over the ensuing 12 hours, a fever of 38.3°C (101°F) developed, with pain, swelling, and erythema of the right shoulder, right knee, and proximal interphalangeal joint of the right fourth toe. Physical findings were otherwise unchanged from those noted previously.

Stool examination was again negative for *Yersinia, Campylobacter, Shigella,* and *Salmonella* species, *Staphylococcus aureus,* and ova and parasites. Stool culture grew *C difficile,* and *C difficile* toxin was identified. Colonoscopy showed patchy colitis without pseudomembranes. Several colon biopsy specimens were obtained that showed a nonspecific colitis without features of ulcerative colitis or Crohn's disease. HLA typing was positive for B27.

The patient was treated with vancomycin, 500 mg orally every six hours, and ibuprofen, 600 mg four times a day. His symptoms rapidly disappeared, and he remained asymptomatic following a seven-day course of therapy.

Discussion

Reactive arthritis is a well-recognized sequela of a variety of gastrointestinal disorders that include inflammatory bowel disease, jejunoileal bypass, and various gastrointestinal infections, including those caused by *Salmonella, Shigella, Yersinia,* and *Campylobacter* species and *Strongyloides stercoralis, Taenia saginata,* and *Ancylostoma duodenale.*[1]

Antibiotic-induced pseudomembranous enterocolitis has become common and widespread with the increasing use of broad-spectrum antibiotics. In 1977 Larson and coworkers identified a fecal toxin neutralized by *Clostridium sordellii* antitoxin as the cause of antibiotic-induced pseudomembranous enterocolitis,[2] and soon afterward en-

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terotoxin-producing strains of *C difficile* were identified as the source of this toxin.[3] Although pseudomembranous enterocolitis induced by *C difficile* is now commonly recognized, reactive sterile arthritis associated with this disorder has been rare. Several cases of reactive arthritis associated with pseudomembranous enterocolitis were reported before the discovery of *C difficile* that had the characteristic history of this disorder.[4,5] In 1980 Fairweather and associates reported a case of reactive arthritis associated with documented *C difficile*-induced enterocolitis.[6] Since then there have been scattered reports in the English-language literature.

Reactive arthritis induced by *C difficile* typically presents as an asymmetric oligoarthritis or polyarthritis of predominantly the large joints, occurring one to two weeks after the onset of the enteral infection. The arthritis may be migratory and appear as an enthesopathy predominantly involving tendons and their insertions.[4,7] The arthritis can last from weeks to years, and there may be other nongastrointestinal manifestations associated with it. Urethritis with *C difficile* reactive arthritis was described by Hayward and colleagues.[8] The classic triad of Reiter's syndrome—urethritis, conjunctivitis, arthritis—has been described in 2 of the 15 cases reported to date.[9,10] Iritis and pleuritis have been described with *C difficile*-induced reactive arthritis, but the skin, cardiac, and neurologic manifestations of reactive arthritis associated with other infections have not been reported.[7,10]

The exact mechanism through which reactive arthritis occurs is unclear. It has been postulated that systemic absorption of *C difficile* toxin with resultant antibody production may be important in the pathogenesis of reactive arthritis associated with *C difficile*-induced enteritis. In reactive arthritis induced by *Salmonella* species, the severity of the arthritis appears to fluctuate with the levels of *Salmonella* antibodies,[11] and in inflammatory bowel disease the severity of the arthritis appears to correlate with the level of circulating immune complexes.[12] Urticaria has occurred before the onset of arthritis associated with *C difficile*-induced diarrhea, supporting an immune-complex cause.[4,13] Antitoxin has been shown in 2 patients with *C difficile*-induced reactive arthritis,[6,14] but not in 11 others with *C difficile* enterocolitis without arthritis.[6] This further suggests that the cause of arthritis is immune-complex disease or antibody cross-reactivity with synovial tissue. *Clostridium difficile*-induced reactive arthritis, however, has not been described with the other signs or symptoms associated with immune-complex disease, and there are cases of *C difficile*-induced reactive arthritis occurring without the presence of antitoxin.[8,9] In this patient the presence of antitoxin was unfortunately not determined.

The association of HLA-B27 with postinfectious Reiter's syndrome and reactive arthritis following infection with *Salmonella, Shigella,* or *Yersinia* species is clear, occurring in 80% to 90% of the cases.[15] It is speculated that HLA-B27 is a marker for an immune response gene determining susceptibility to an environmental trigger for reactive arthritis. The role of HLA-B27 in *C difficile*-induced reactive arthritis is unclear. The patient described herein was HLA-B27-positive. Although the number of cases reported in the literature is small, *C difficile*-induced reactive arthritis appears to be associated with HLA-B27 in 10 of 15 patients (66%).[7-10,13-19]

The success of the treatment of *C difficile*-induced reactive arthritis has been variable, with symptoms resolving in two weeks to two years. Cope and co-workers suggested a correlation between the presence of HLA-B27 and prolonged arthritis in patients with *C difficile*-induced diarrhea. Review of all the published cases does not support this assumption.[6-10,13-19] A wide variety of anti-inflammatory agents has been used in the treatment of *C difficile*-induced reactive arthritis, including oral adrenocorticosteroids, intra-articular adrenocorticosteroids, and nonsteroidal anti-inflammatory agents with the last used most often. Although the course of the arthritis does not clearly correlate with the resolution of diarrhea or the eradication of *C difficile* and toxin from the stool, it appears to be shorter in patients treated with oral vancomycin. In the case reported herein, there was a definite correlation between the resolution of the patient's gastrointestinal symptoms with oral vancomycin therapy and that of his reactive arthritis, as has been shown in another patient with relapsing *C difficile*-induced reactive arthritis.[8]

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Acquired Hemophilia in a Patient With Myeloma

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ABNORMAL BLEEDING IS frequently associated with dysproteinemias. Abnormalities that account for the bleeding tendency in patients with these disorders include thrombocytopenia, impaired platelet function, and the hyperviscosity syndrome. Abnormally low rates of synthesis of specific plasma coagulation factors, or the genesis of inhibitors to these factors, are also involved. A single patient may have more than one coagulation abnormality.[1-3] The following case is the first reported association of a factor VIII inhibitor with the λ-light-chain form of myeloma.

Report of a Case

The patient, a 58-year-old woman, had weakness, fatigue, and anorexia for three weeks. Since the age of 20, she had smoked about 40 cigarettes and drunk 9 fl oz (266 ml) of whiskey a day. She had been taking fenoprofen calcium for many years for knee pain. Examination revealed orthostatic changes in blood pressure—from 130/60 mm of mercury supine to 100/50 mm of mercury standing—obesity, a grade I/VI systolic ejection murmur heard over the left sternal border, a skin rash in the left inguinal region with mild excoriation and drainage, clubbing of the fingernails, external hemorrhoids, and occult blood in the stool. The other physical findings were normal.

On admission, the hemoglobin level was 58 grams per liter (5.8 grams per dl), the mean corpuscular volume was 65.5 fl (65.5 μm^3), the leukocyte count was 9×10^9 per liter (9,000 per mm^3) with a normal differential cell count, and the platelet count was 276×10^9 per liter (276×10^3 per mm^3). The reticulocyte fraction was 5×10^{-3} (0.5%), and a peripheral smear showed microcytic, hypochromic, and target erythrocytes. A prothrombin time and an activated partial thromboplastin time (aPTT) were within normal limits. Abnormal blood chemistry and urine values are shown in Table 1.

Serum protein electrophoretic analysis showed a low albumin level of 27 grams per liter (2.7 grams per dl) (normal, 32 to 50), a γ-globulin level of 11 grams per liter (1.1 grams per dl) (normal, 7 to 15), and a small monoclonal spike in the γ-globulin region. Immunoelectrophoresis showed a free λ-light-chain monoclonal gammopathy with suppression of all other components of the immune globulin system.

TABLE 1.—*Abnormal Laboratory Values at Initial Presentation*

Substance	Patient Values: SI Units	Patient Values: (Conventional Units)	Normal Values*
Blood Chemistry			
Urea nitrogen, mmol/liter (mg/dl)	22.1	(62)	1.8 to 8.9
Creatinine, μmol/liter (mg/dl)	260	(4.1)	45 to 120
Uric acid, μmol/liter (mg/dl)	1,250	(21)	130 to 460
Calcium, mmol/liter (mg/dl)	1.90	(7.6)	2.12 to 6.62
Phosphorus, mmol/liter (mg/dl)	1.75	(5.4)	0.80 to 1.45
Alkaline phosphatase, U/liter (IU/liter)	155	(155)	50 to 136
Total protein, grams/liter (grams/dl)	52	(5.2)	60 to 85
Urine			
Protein reaction	4+		
Creatinine clearance, ml/sec (ml/min)†	0.40	(22)	1.18 to 1.92
Total protein, grams/d (mg/24 hr)†	5.90	(5,900)	0.70

SI = Système International

*Normal values are given in SI units.
†Based on a 24-hour collection.

Urine protein electrophoretic analysis revealed a large monoclonal spike in the mid-γ-globulin region and an elevated total protein level of 2.6 grams per liter (260 mg per dl) (normal < 0.30) composed of 5% albumin and 95% γ-globulin. Immunoelectrophoresis demonstrated a massive excretion of free λ-light chain-type Bence Jones protein; the particular analysis indicated a total value for reactive protein of 1.77 grams per day (1,765 mg per 24-hour specimen) (normal < 0.2), of which 96% was γ-globulin.

A bone marrow examination revealed increased cellularity, normoblastic erythroid hyperplasia, moderate plasmacytosis (22%), and no stainable iron stores. X-ray films of the long bones and pelvis showed no osteolytic lesions. A lytic lesion in the lateral end of the left clavicle was noted on a chest film. A colonoscopy was normal. Esophagogastroduodenoscopy revealed a partially healed benign gastric ulcer.

The patient was hydrated and treated with packed red blood cell transfusions and ferrous sulfate. Because λ-light-chain myeloma was clearly present, chemotherapy was initiated with melphalan, 0.25 mg per kg of body weight orally daily for five days, and prednisone, 1.0 mg per kg orally daily for five days, and this regimen was repeated every four weeks. After six cycles of chemotherapy, the patient's condition improved with the urine protein excretion decreasing to 0.15 grams per day (150

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ABBREVIATIONS USED IN TEXT

aPTT = activated partial thromboplastin time
Ig = immunoglobulin

mg per 24 hours); the hemoglobin level becoming stable at 105 grams per liter without transfusions; and renal function improving, with a decline in the creatinine level to 130 μmol per liter (1.5 mg per dl). She was stable without further chemotherapy at this time and refused further diagnostic tests or regular follow-up.

The patient returned at age 62 because she had coffee-ground emesis. Physical examination on admission to the hospital revealed that she was moderately obese but in no apparent distress. The liver was palpated 2 cm below the right costal margin, and stool was positive for occult blood. Initial laboratory data included a hemoglobin level of 73 grams per liter (7.3 grams per dl), a leukocyte count of 5.1×10^9 per liter (5,100 per mm^3), with a normal differential cell count, a platelet count of 225×10^9 per liter (225×10^3 per mm^3), a prothrombin time of 12.9 seconds (control, 12.0), aPTT 64.7 seconds (control, 30.6), blood urea nitrogen 6.4 mmol per liter (18 mg per dl), and creatinine 97 μmol per liter (1.1 mg per dl). Urine protein electrophoresis showed a monoclonal spike in the γ-globulin region (71.4% of total protein) with a total urinary protein level of 0.535 grams per day (535 mg per 24 hours). Urine immunoelectrophoresis demonstrated excretion of a large quantity of monoclonal λ-light chains.

Esophagogastroduodenoscopy showed six gastric ulcers, so ranitidine was administered. The patient also received transfusions with packed red blood cells and whole blood. Her gastrointestinal bleeding ceased. Because of a lack of accessible peripheral sites, specimens for initial blood tests were obtained by left femoral venipuncture, and on the fourth day thereafter a small hematoma was noted in the left groin. Over the next 24 hours the patient had palatal oozing, and the inguinal hematoma expanded despite tamponade of the area. Pulses of her left leg were palpable, but the hemoglobin level decreased to 68 grams per liter. A hematologic consultation was obtained. Additional coagulation tests were recommended, and these revealed an Ivy bleeding time of 6 minutes (normal, 2.3 to 9.5), a platelet count of 134×10^9 per liter, an aPTT of 73.9 seconds (control, 30.9) that decreased to 40 seconds in an immediate 1:1 mix with normal plasma but increased to 57 seconds after 60 minutes of incubation. Factor VIII activity was 8.2% of normal, and a factor VIII inhibitor titer of 36 Bethesda units per ml was obtained.

Immunosuppressive therapy with oral prednisone, 100 mg per day, and oral cyclophosphamide, 100 mg per day, was initiated. In addition, human factor VIII (antihemophilic factor) concentrate was administered intravenously at the rate of 43 units per kg every six hours. The palatal bleeding ceased, and the inguinal hematoma became stable. Coagulation test results gave indications of improvement, with an increase in the apparent plasma factor VIII activity to 25% and a decrease in the factor VIII inhibitor titer to 2.0 Bethesda units per ml. On day 9, however, the inguinal hematoma dramatically increased in size, and there was evidence of superficial skin necrosis. The factor VIII inhibitor titer increased again to almost pretreatment levels (14 Bethesda units per ml). Human factor VIII therapy was discontinued, and porcine factor VIII (Hyate:C, Porton Products Ltd, Van Nuys, California) was administered by intravenous infusion at an initial rate of 100 units per kg, followed by 57 units per kg every six hours. This therapy resulted in the cessation of bleeding and correction of the coagulation abnormalities with factor VIII activity of 89.3%. The next day a surgical procedure was done without complications to evacuate the inguinal clot and debride the wound. Cyclophosphamide and prednisone were discontinued to reduce the risks of infection and impaired wound healing after the operation. She continued to receive intravenous hydrocortisone and diphenhydramine hydrochloride before porcine factor VIII transfusions to reduce the risk of anaphylaxis.

The patient had an uneventful postoperative course until day 16, when acute abdominal pain developed. An abdominal film revealed free intraperitoneal air. During an exploratory laparotomy, a perforation of the cecum with peritonitis was found, and the patient underwent a right hemicolectomy and ileostomy. Examination of the surgical specimens revealed acute and chronic hemorrhagic colitis and pericolitis with perforation involving the cecum, diffuse colonic mucosal hemorrhages consistent with a bleeding diathesis, acute and chronic peritonitis, and diffuse mucosal hemosiderosis. After the operation the patient required mechanical ventilation support, and cefoxitin was administered for the treatment of the peritonitis. Porcine factor VIII therapy was continued, and no further bleeding was noted.

On day 24 wound dehiscence and evisceration developed, and the patient returned to surgery for repair of the evisceration. At the time of reexploration, no abscess was noted and the peritonitis had cleared. Porcine factor VIII therapy was discontinued because plasma factor VIII activity had declined to 10.3% of normal, and an inhibitor to porcine factor VIII had developed with a level of 2.75 Bethesda units per ml. She had thrombocytopenia with platelet counts as low as 16×10^9 per liter and a prolonged prothrombin time of 16.6 seconds (control, 11.0). Factor IX complex human concentrate (Konyne-HT Cutter Biologics/Miles, West Haven, Connecticut) transfusions were administered, initially at 55 units per kg followed by 109 units per 24 hours in four divided doses, which shortened the prothrombin time. The platelet counts increased after platelet transfusions.

The rest of the hospital course was one of progressive generalized deterioration. Intra-abdominal bleeding and renal insufficiency developed with elevations of the creatinine level to 390 μmol per liter (4.4 mg per dl) and the blood urea nitrogen to 34.6 mmol per liter (97 mg per dl). Progressive respiratory failure ensued, and the patient died on the 28th hospital day.

Discussion

Acquired inhibitors of blood coagulation, also known as circulating anticoagulants, are endogenously produced pathologic substances, usually immunoglobulins, that either react directly with clotting factors or inhibit their reactions.[3] In patients without hemophilia, a circulating antibody against the factor VIII coagulant protein is a rare finding, occurring in 1 of 5 million people,[4] but it is the most common cause of spontaneous acquired inhibition against a clotting factor.[5] Factor VIII inhibitors have most often been associated with collagen vascular diseases, drug allergy, skin disorders, malignant neoplasms, and in the postpartum period.[5-7] In some cases acquired factor VIII inhibitor is the primary cause of illness; in one survey 46% of patients with this disorder were otherwise healthy, usually elderly persons.[7] Circulating anticoagulants against factor VIII have occasionally been reported with plasma cell dyscrasias, occurring with immunoglobulin (Ig) A myeloma,[8] Waldenström's macroglobulinemia,[9] amyloidosis,[10] and in a patient with an IgM paraprotein in whom chronic lymphocytic leukemia later developed.[11] This case is the first reported of a factor VIII inhibitor associated with λ-light-chain myeloma.

Autoantibodies against factor VIII are predominantly IgG, frequently from the IgG4 subclass, and have a preponderance of κ-light chains.[4] Alternatively, the factor VIII antibodies associated with plasma cell dyscrasias have been monoclonal IgA[8,10] and IgM,[9] with monoclonal λ[9] and κ[10] light chains. Antibodies inhibit or neutralize factor VIII activity by blocking functional epitopes or antigenic sites on the factor VIII protein.[4] Deletion mapping studies using recombinant DNA methods have indicated considerable epitope heterogenicity among factor VIII inhibitor antibodies, but most share one or both antigenic determinants in two regions of the factor VIII protein.[12] Although the factor VIII autoantibody in the present case has not been isolated, we speculate that the patient's monoclonal λ-light chain had activity against specific epitopes on the factor VIII molecule. Factor VIII inhibitors are characteristically time and temperature dependent in laboratory assays; for example, the incubation of inhibitor plasma mixed with equivolume normal plasma at 37°C for two hours or longer enhances the expression of factor VIII autoantibodies.[4] The patient's inhibitor in this report followed this characteristic pattern.

The clinical presentation of the patient in this report is consistent with that of other patients with acquired hemophilia who may have spontaneous hemorrhage into muscles or joints, ecchymoses, hematuria, melena, intracranial and retroperitoneal hemorrhage, intractable epistaxis, or persistent bleeding after an operation or minor trauma. In one survey, 87% of the patients had major bleeding, and death was attributed, directly or indirectly, to the presence of the inhibitor in 22% of the cases.[7]

The optimum management of patients with acquired factor VIII inhibitors who have an acute hemorrhage is not well established. Various therapeutic options have been tried, including high doses of human factor VIII concentrate to neutralize the inhibitor and provide a plasma factor VIII level of at least 0.3 U per ml (30%),[13] plasmapheresis to remove the antibody,[13] and prothrombin complex concentrate and activated prothrombin complex concentrate to provide procoagulant activity that bypasses the factor VIII-dependent clotting reactions.[14] 1-Deamino-8-D-arginine vasopressin use has also been recommended as a beneficial and less expensive treatment of patients with acquired factor VIII inhibitors.[15] These treatment methods may be successful in certain instances, but the failure rate is high.[13]

A more recently introduced and effective therapy involves transfusion with porcine factor VIII. The rationale for its use in patients in whom factor VIII circulating anticoagulants develop is based on the reduced cross-reactivity of the inhibitors for porcine factor VIII compared with human factor VIII.[16] One study reported good or excellent responses with regard to pain relief and a reduced number of hemorrhagic sites in 82% of patients with acquired hemophilia who received porcine factor VIII. Two patients, however, generated porcine inhibitors to levels in excess of 10 Bethesda units per ml.[17] This study and others supported the use of porcine factor VIII as safe and clinically effective in the treatment of hemorrhage due to factor VIII inhibitors.[18,19] The patient in this report also had an excellent clinical response to porcine factor VIII with a pronounced rise in plasma factor VIII activity and the cessation of bleeding; later, however, an inhibitor to the porcine factor VIII developed that rendered it ineffective. Another limitation in the use of porcine factor VIII is the development of thrombocytopenia, which may be the result of increased platelet aggregation demonstrated by platelet clumps on peripheral blood smear.[20] The absence of platelet clumps on the peripheral smear of this patient suggests that the thrombocytopenia was not due to porcine factor VIII; therapy with antibiotics and cyclophosphamide and the presence of peritonitis are other possible causes.

Early, largely anecdotal reports recommended immunosuppressive therapy for factor VIII inhibitors with the intent of eliminating or suppressing the cell clone responsible for inhibitor synthesis. Preliminary results from a controlled, prospective, randomized trial to evaluate the therapeutic effects and side effects of cyclophosphamide and prednisone alone or in combination in eliminating or decreasing the titer of factor VIII autoantibodies indicate that even patients with titers greater than 5 Bethesda units per ml may respond to immunosuppressive therapy, but more studies are needed to determine the optimal treatment of various clinical categories.[21] Although ineffective in the treatment of inhibitors associated with hemophilia, another therapeutic approach aimed at suppressing the production of the inhibitor with varying results in patients with acquired hemophilia is the administration of high doses of intravenous immune globulin G.[22] Our patient had a temporary response to immunosuppressive therapy and human factor VIII transfusion.

Although factor VIII inhibitors in association with dysproteinemias are relatively rare, they are of consider-

able clinical import because of the dramatic clinical presentations and the need for early and accurate diagnoses. The advanced age of most of these patients further increases the morbidity and mortality. Recent therapies have improved the results for some patients. The rarity of the disease limits the opportunity for clinical trials and necessitates the report of individual cases until better guidelines for treatment can be formulated.

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Topics in Primary Care Medicine

Factitious Physical Disorders

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Factitious means willfully produced by humans. The term factitious physical disorders applies to medical conditions that are fabricated by patients. The best-known factitious disorder is the Munchausen syndrome. This condition was described by Asher in 1951 and was applied to patients who made a career of manufacturing diseases. They were often sociopathic imposters who traveled from hospital to hospital without interruption.

Current studies suggest, however, that Munchausen syndrome applies to only 10% of patients with factitious disorders.[1] The remainder include persons who only episodically produce disease states, often after serious life stressors. They often come from stable families, have jobs, and appear reasonably well adjusted. I will not discuss factitious psychological disorders that are typically seen only in psychiatric settings. The American Psychiatric Association's diagnostic criteria for factitious illness with physical symptoms are the following[2]:

- Intentional production or feigning of physical (but not psychological) symptoms.
- A psychological need to assume the sick role, as evidenced by the absence of external incentives for the behavior, such as economic gain, better care, or physical well-being.
- Does not occur exclusively during the course of another major psychiatric disorder, such as schizophrenia.

Patients with factitious disorders can and have produced signs or symptoms of virtually any disease. The level of production can vary from a purely fictitious medical history (lying about symptoms), a simulation of signs or symptoms (such as heating a thermometer to simulate a fever), to the actual production of disease states (administering bacterial cultures intravenously to produce septicemia). Almost all laboratory abnormalities can be produced factitiously. The only limits to factitious disorders are those of human creativity.

There are usually clues to the presence of a factitious disorder. Patients with the Munchausen syndrome have a long and continual succession of hospital admissions that are revealed with further investigation. Other patients with factitious disorders may reveal themselves by reproducing puzzling and unusual or inconsistent clinical situations. Examples include elevated temperatures without corresponding heart rate changes or polymicrobial sepsis without any apparent focus of infection. An important clue to the presence of factitious disorders is that the patient or a family member works in the health field (more than 75% of cases). Common occupations include nurses, ward clerks, medical receptionists, and laboratory technicians. Another important clue to the presence of a factitious disorder is that the patient's concern about the seriousness of the illness appears to be less than the physician's.

General physicians need to have a high index of suspicion when clues to a factitious disorder present themselves. The average factitious disorder is not accurately diagnosed for a period of five to ten years after it first occurs. The social effects of factitious disorders can be substantial. They can produce serious disability, and the financial costs can be enormous. In one case of factitious disorder, hospital charges alone amounted to more than $400,000 in one year.

The differential diagnosis for factitious disorders includes unusual authentic diseases. After these have been ruled out, the differential expands to other forms of abnormal illness-affirming behavior in which patients produce signs or symptoms out of proportion to the disease that is originally present.[3] Malingering is an important state to consider. Malingerers are similar to patients with factitious disorders in that they consciously produce their signs and symptoms. They differ in that their production is stimulated by a conscious motivation such as obtaining money, drugs, or relief from a noxious situation. Another way of differentiating patients with factitious disorders from malingerers is that the only overt motivation for the behavior that an outside observer can determine is that of achieving the patient role. The factitious behavior, although consciously produced, is motivated by unconscious factors. This is similar to patients with a phobia who consciously avoid the phobic object without knowing why they do so.

Other abnormal illness-affirming behaviors can be similar to factitious disorders. Conversion reactions, somatization disorders, somatoform pain, and hypochondriasis all have unconscious motivations. They differ from factitious disorders in that their production, as well as their motivation, is unconscious. These patients do not believe they have produced their signs or symptoms, which contrasts with patients with factitious disorders who know they have done so but do not know why.

(Eisendrath SJ: Factitious physical disorders. West J Med 1994; 160:177-179)

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The cause of factitious disorders derives from the unconscious motivations that stimulate the behavior. Many of these have their roots in the patients' childhood development and current life stressors. Many patients with factitious disorder have experienced such childhood deprivation that medical care and admission to a hospital represent a socially sanctioned way to obtain care during times of stress. Others use this as a way to achieve a sense of mastery over a traumatic experience earlier in their life. For example, persons who felt no control over a childhood operation may recreate an illness situation that they do control, even if they must suffer as a consequence. Another frequent motivation for factitious disorders involves a sense of guilt and masochism. Persons who feel guilt over sexual impulses, for example, may produce an illness as a form of self-punishment or as a way to avoid a sexual relationship.

The treatment of factitious disorders is challenging for all involved. When a factitious disorder is suspected or the diagnosis has been confirmed, a psychiatric consultation should be obtained. Once the diagnosis has been confirmed, it is helpful to have a staff meeting with all caregivers involved. Staff members need to be given an opportunity to express their anger after a factitious disorder has been identified. Patients with these disorders have deceived their caregivers and violated one of the primary conditions of the socially accepted sick role by not attempting to get better. Once the naturally occurring anger has been discussed, a treatment intervention can be designed.

Two broad alternative approaches should be considered. The first involves the primary physician and the psychiatric consultant meeting with the patient.[4] The primary physician confronts the patient in a nonpunitive manner with the evidence that the illness is factitious, possibly as follows: "We know that you have been producing your illness, and we feel that you have been doing this as a way to get help for some problem in your life. We want to get you that help in the most appropriate way and want you to get psychiatric treatment." The psychiatrist then becomes actively involved in getting the patient to accept a psychiatric treatment program as either an inpatient or an outpatient. If a psychiatric condition such as major depression has been identified in association with the factitious disorder, this is addressed as part of the treatment.

In our experience, the above-described nonpunitive confrontation is of limited value. It often does little except humiliate the patient and drive the patient to another facility or caregiver. In our program we have developed alternatives to overtly confronting patients about the factitious nature of their disorder.[5] A primary feature of our approaches is an attempt to provide patients with face-saving ways to relinquish their symptoms without having to acknowledge the nature of their disorder publicly.

One such strategy is to inform patients that we believe they have a serious problem that has not yielded to conventional medical care and requires something further. For example, a woman with a factitious wound-healing problem was offered hypnosis to improve the flow of blood, oxygen, and natural healing in the tissues. This approach allowed her to improve while she engaged in treatment with a psychiatrist without having to acknowledge the cause of her condition. Biofeedback and hypnosis are excellent treatment options for patients who need a rational way to explain how they can get better without having to admit the sham nature of their disorder.

Another approach is to offer patients an inexact interpretation of their problem that omits confronting them about the factitious cause. This involves conveying to a patient something like "We believe your problem is related to psychological factors in some way. We would like you to work with a psychiatrist while we continue to work on the medical aspect." We explain that this type of condition is common and give examples of psychophysiologic conditions such as peptic ulcer disease so that the patient can accept a psychiatric referral. We do not explicitly tell patients that we believe they produced their disorder. We also do not threaten patients with abandonment. For example, this approach worked well with a female nurse who developed a cellulitis whenever she became sexually involved with men. She had a history of having been sexually abused as a teenager, which had led to her feeling anxious and guilty whenever she began to have a sexual relationship. When we told her that we thought her condition was related to psychological factors but not that we believed it was factitious, she accepted a psychotherapy referral. Many patients can accept psychiatric referral when they do not feel overtly threatened with disclosure. Many of these patients have engaged in psychotherapy and then voluntarily revealed the factitious techniques they employed.

Some physicians may think they are jeopardizing the physician-patient relationship if they do not completely disclose their diagnosis to their patients. In our experience with these patients and with those with other abnormal illness-affirming conditions such as hypochondriasis and somatization, the level of disclosure must be adjusted by the physician's assessment of a patient's ability to use the information in a beneficial manner. In addition, it must be remembered that patients with factitious disorders are already aware of their role in producing their disease, so that full disclosure does not add new information to the patient.

Another strategy involves presenting patients with a differential diagnosis for their disorder. In this differential diagnosis, we include a factitious cause as one possibility. We then outline treatment alternatives and suggest that certain results will tell us whether or not the disorder is factitious. For example, one patient had an extremity wound that did not heal for several years. We told her that if a forthcoming skin flap was not successful, it would mean to us that her disorder was factitious. Given this choice, the flap was successful for the first time despite numerous previous attempts and overt confrontation at another institution. The differential diagnosis allowed her a face-saving way to heal the wound without admitting the cause.

Factitious disorders represent patients' maladaptive attempts to cope with life stressors. Whereas patients with the Munchausen syndrome have an intractable form of factitious disorder, most patients have more treatable conditions. Nonetheless, to achieve success, treatment approaches need to be as creative as the patients who produce the disorders.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

STEPHEN J. McPHEE, MD
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HUNTINGTON'S DISEASE

Poor Mr. Z.
His little fedora isn't on straight.
He jumps and jerks in his chair, as if possessed.
Eyebrows dance beneath a wrinkling forehead.
He smiles and frowns, smiles and frowns, smiles and frowns.
His worried wife now ponders the skeletal frame
of the once plump salesman whose handshake
sold a thousand cars.
He tries attending to our words,
interjecting a joke between hiccups and snorts.
His brain has a mind of its own
different from his own mind, vaguely aware
of the fate waiting down the long dark hallway
he now walks in his disjointed stumbling way,
careening slowly toward the end.

THOMAS D. BIRD, MD©
Seattle, Washington

Commentary

Death of a Doctor

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What quality of care will physicians receive from colleagues when they face their final hour? Will they be treated as Jim was?

Jim was my friend for 34 years. His generosity, compassion, and infectious enthusiasm had few boundaries. He was devoted to patients in his large general practice in this small southern California coastal city, responding to their needs day and night. Many, born with his help, remained his patients and, in turn, gave birth to their own children for whom he provided continuing care. The local private community hospital was a continuous beneficiary of his support and loyalty.

Jim began to experience shortness of breath at higher altitudes of the Sierra, consulted a physician specialist in pulmonary diseases, and was treated with steroids. His condition steadily worsened, and the terrible diagnosis was made—progressive idiopathic pulmonary fibrosis. The cause is unknown, and there is no specific treatment. The process was relentless. Steroids caused demineralization of his skeleton. He soon required a cane to walk short distances.

Jim's physician told him he was "grasping at straws" if he thought there was anything else to be done, and he, the physician, was spending too much time with this problem, and Medicare was complaining about the cost. (Traditionally, Jim and most physicians of his generation have taken care of colleagues, their families, nurses, and members of the clergy free of charge.) Jim, deeply offended, felt he could not remain under the care of such a physician.

Aware of Jim's plight, I gained his permission to call a prominent pulmonologist from another community. Jim was admitted to a hospital at once. In addition to his primary pulmonary problem, he suffered steroid poisoning. Critically short of breath and emotionally devastated, he was saddened over not being in his cherished local hospital. His new physician did not have privileges there and possibly would not have gone there anyway.

During his short period in the hospital, Jim's condition steadily worsened. Oxygen was provided around the clock. His family maintained a vigil at his bedside. I visited him frequently and, to my astonishment, found his physicians were apparently too busy to attend to his needs for adequate medical and emotional support. His family was reluctant to call his doctor when there were questions about his acute distress. His wife seemed to be intimidated by the physician and his partners. I called his doctors on several occasions, asking for attention to Jim's desperate condition. Usually these calls were not answered for hours. In the meantime, Jim suffered, gasping for air for hours each day, he and his family panic-stricken.

His admitting physician had left his patient for several days to attend an out-of-town computer meeting for the hospital. His partners displayed no real interest in Jim, his problems, or those of his family.

Jim died of suffocation.

Could sympathy, compassion, and concern for physical and emotional distress have been neglected in the medical training of some younger physicians? Perhaps physicians who cannot, or will not, include these qualities in the care of their patients are not solely to blame for such omissions.

It is too easy to share responsibility for a diagnosis or outcome with results from million dollar instruments and the highly skilled, narrowly trained physicians in charge of them. Yet, those "superspecialists" are seldom, if ever, able to offer needed comfort and emotional support to patients and their family members.

This serious, complex, and important problem deserves attention from all physicians and medical educators:

- Are medical schools to blame? Are there defects in the selection process for medical students?
- Are older practicing physicians to blame? Positive example can be a powerful teaching tool in human behavior.
- Could greed be driving physicians to the most efficient use of their time at the expense of quality care for their patients?
- Should the often-expressed "time is money" be an acceptable guide for physicians as they administer medical care?

There is hope. Some medical schools now require students to spend a few days in hospital wards as patients. The goal is to increase sensitivity to the concerns and apprehensions of patients and their family members.

Perhaps, as medical fees moderate, greater importance will be placed on conscientious, considerate, and sympathetic care by physicians. Final answers must lie within the heart of each physician.

Again, the question: What quality of care will physicians receive from colleagues when they face their own final hour? Will care be any better than that received by my friend Jim?

(Johnston DG: Death of a doctor. West J Med 1994; 160:180)

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Editorials

Cytokines, Neuropeptides, and Other Factors in Cutaneous Immune Responses

A BROAD SPECTRUM OF immunologic processes involving numerous cellular constituents and products of the skin has been identified in recent years. Ranging from the participation of cytokines in the pathophysiology of psoriasis, to the recently described contribution of mast cells to the production of cytokines, to the elucidation of the processes involved in the adhesion of leukocytes to dermal endothelial cells and their subsequent emigration out of the vasculature, progress in understanding cutaneous function and disease has been closely linked to progress in understanding immunologic and inflammatory processes in the skin. In this issue of the journal, Salmon and co-workers review the principal elements that have clearly established the role of the skin as an organ of immunity.[1] They have focused their attention on the properties of the various cellular components of the epidermis and their contributions to immunologic responses of the skin. As these authors observe, a variety of normal and infiltrating cellular constituents of the epidermis—including keratinocytes, melanocytes, dendritic epidermal T cells and epidermotropic T lymphocytes, and Langerhans cells—are active participants in an integrated system that provides protection against external environmental toxins, infections, and the development of cutaneous neoplasms.

Although only a minority with respect to numerical representation in the epidermis, the Langerhans cell is the linchpin in skin-directed immunologic responses. Langerhans cells are unmatched in their versatility in communicating with neighboring structures and with critical components of the immune system. They are able to receive signals, process them, send signals to their surroundings, and migrate out of the epidermis. These unique features make them key elements in pathologic conditions such as cutaneous delayed-type hypersensitivity responses and graft-versus-host reactions. Langerhans cell migration and the subsequent stimulation of resting T cells in adjacent lymph nodes critically depend on the regulated expression of a number of cell-surface proteins. The functional maturation of Langerhans cells into potent antigen-presenting cells during short-term in vitro cell culture has been established as a valid model for the events and changes that occur during their migration from the epidermis to the draining lymph nodes.[2] Several recent reports further confirm this notion and bring into focus the multiplicity of events and complexity of processes involved in Langerhans cell migration and maturation into extremely potent antigen-presenting cells. A report that has generated substantial interest among investigators of antigen presentation and T-cell activation is that presented by Larsen and associates.[3] These investigators have recently shown that the expression of the costimulatory molecule B7-1 is notably induced on the cell surface of Langerhans cells during their functional maturation in cell culture. The induced expression of B7-1 molecules by Langerhans cells is biologically important because B7-1 has been identified as the counter-receptor for T cell-expressed CD28 and CTLA-4, receptors involved in the optimal stimulation of proliferation and cytokine release by $CD4^+$ T cells. Thus, the acquisition of expression of this costimulatory molecule is directly correlated with Langerhans cell maturation into potent antigen-presenting cells.

A second recent important observation—by Tang and colleagues—describes the expression by Langerhans cells of E cadherin, a homophilic adhesion molecule expressed by epithelial cells, such as keratinocytes, that is functionally important in epithelial cell homotypic adhesion and in the progression of epithelial cell carcinomas.[4] Cadherins had not previously been implicated in immunologic processes, such as immune cell trafficking. These investigators demonstrated that freshly isolated Langerhans cells express cell-surface E cadherin, that these cells can adhere to keratinocytes in vitro, and that during short-term culture, E-cadherin surface expression by Langerhans cells is markedly and functionally reduced. This reduction in E cadherin likely facilitates the migration of Langerhans cells out of the epidermis. Thus, it would appear that the migration and assumption of potent immunostimulatory properties by these cells critically depend on the inhibition of adhesion molecules and the concomitant increased expression of costimulatory molecules, and both of these processes must be highly coordinated.

Another clue for the unique ability of Langerhans cells to receive and send signals in a distinctive manner comes from the report of Hosoi and co-workers in which they describe the ultrastructural association of the neurotransmitter calcitonin gene-related peptide (CGRP), which is present in epidermal nerves, with resident Langerhans cells in the epidermis.[5] In addition, these investigators showed that CGRP is able to inhibit Langerhans cell antigen presentation in various in vitro functional assays. This observation yields another intriguing piece in the as-yet-unfinished but fascinating puzzle concerning the relationship between the skin immune system and the nervous system. Among neuroimmunologists and cutaneous immunologists, this relationship has drawn increasing attention that has been fueled by the obvious influence of psychological and psychiatric diseases on skin diseases such as psoriasis and atopic dermatitis.

The fine tuning of the functions and cellular interactions of Langerhans cells within their microenvironment is likely provided by various signal-transducing substances, such as cytokines, growth factors, and chemokines. These soluble peptides perform critical roles in the complex network of events involving the cellular constituents of the immune system in the skin. The complexity of this network is underscored by recent advances in our understanding of the spectrum of abnormalities ob-

served in psoriasis. Cytokines, growth factors, and chemokines that have been implicated in the pathophysiology of psoriasis include, but certainly are not limited to, interleukins-1, -2, -6, and -8, tumor necrosis factor (TNF)α, transforming growth factor (TGF)α, and interferon (IFN)-γ. These substances are thought to be synthesized and released by various bone marrow-derived and non-marrow-derived cellular constituents of the skin, including Langerhans cells, infiltrating $CD4^+$ T cells, keratinocytes, dermal microvascular endothelial cells, and dermal dendrocytes. One model for the initiation of this cascade of events is through the stimulation of T cells by Langerhans cells or dermal dendrocytes. The presumptive net effects of this release of a panoply of factors are the initiation of proliferation of keratinocytes, further cytokine expression, and in turn, autocrine and paracrine self-perpetuation of their production. Another effect of the release of these factors is the induction of leukocyte adhesion molecules on the dermal vascular endothelium, leading to the recruitment of additional leukocytes and skin-homing T-lymphocytes (for a review, see Baker and Fry[6]). Thus, psoriasis, which traditionally has been viewed as a disease of dysregulated proliferation of keratinocytes, has now fallen within the purview of autoimmune diseases. Indeed, many of the therapies that have proved effective in suppressing psoriasis, such as methotrexate and cyclosporine, can be viewed as primarily immunosuppressive rather than antiproliferative agents.

To imply that a "smoking pistol" in the pathogenesis of psoriasis has been identified would be a gross oversimplification and premature. Indeed, there is still considerable discussion and controversy concerning initiating events and specific defects in this disease. The conflicting findings and implications concerning the role of IFN-γ, TGFα, and the receptors for these factors in psoriasis provide an appropriate example of the controversies yet to be resolved. Interferon γ induces a number of changes in keratinocyte phenotype and function. Among them is the induction of intercellular adhesion molecule (ICAM)-1, an adhesion molecule that interacts with the cell-surface integrin, lymphocyte function-associated antigen (LFA)-1, which is expressed on virtually all leukocytes, and thus facilitates the physical interaction of keratinocytes with infiltrating T cells and neutrophils. In addition, IFN-γ has been demonstrated to have antiproliferative effects on normal keratinocytes in vitro. Psoriatic keratinocytes, however, are apparently not susceptible to this antiproliferative effect. Scheynius and associates have shown by immunohistochemical techniques "normal" levels (by intensity) of IFN-γ receptors expressed by psoriatic keratinocytes, but receptor expression is limited to the lower half of epidermis, while keratinocytes in normal skin display receptors throughout.[7] On the other hand, in cell suspensions generated from psoriatic and normal skin, Mitra and Nickoloff have shown that keratinocytes from patients with psoriasis overall display decreased levels of radiolabeled-IFN-γ binding in vitro, and this inhibition of receptors can be induced in normal keratinocytes by yet another factor generated within the epidermis, TGFα.[8] The in vivo relevance of this observation is substantiated by the fact that increased TGFα levels have been detected in psoriatic skin at the levels of both messenger RNA and protein expression.[9,10] Further confusing the issue is the recent finding by Nanny and colleagues that topically applied epidermal growth factor (EGF), which like TGFα binds to the EGF receptor, can result in a morphologic resolution of the psoriatic lesion as seen in a murine transplant model.[11] Thus, discrepancies concerning the roles of specific cytokines, growth factors, and their receptors and the definitive determination of which events are causative, consequential, or simply epiphenomenonal remain yet to be resolved. Active and intense investigation into the immunologic aspects of psoriasis are likely to yield additional clues, and perhaps ultimately precise answers, concerning the pathogenesis of this disease.

Another site of interaction of the immune system with the skin is the dermal microvasculature. The endothelial cells of the microvessels that permeate the dermis are strategically placed between the elements of the blood system and the surrounding dermis. In recent years, cell biologists and immunologists have elucidated biologic and immunologic features of these cells that extend far beyond their traditional barrier function between interstitium and blood-borne cells. Vascular endothelial cells produce a variety of proinflammatory cytokines, including interleukins-1, -6, and -8, as well as selected growth factors and chemokines. In addition, these cells are capable of expressing a whole array of adhesion molecules that allow for and direct selective adhesion of immunologically relevant cells that are carried through the bloodstream. Thus, the interplay of cytokines, adhesion molecules, and directed trafficking of leukocytes finds their principal playing field among the microvascular endothelial cells. The most biologically important families of adhesion molecules that are expressed and induced on the luminal surfaces of endothelial cells include those belonging to the immunoglobulin gene superfamily (ICAM-1, vascular cell adhesion molecule [VCAM]-1) and those belonging to the selectin family (E- and P-selectin). A current model of the interaction of the endothelium with leukocytes involves an initial reversible rolling of leukocytes mediated by the increased expression of P and E selectin on endothelial cells.[12] This rolling is followed by the activation of leukocyte-expressed integrins, and these activated integrins then form stable adhesion complexes to endothelial ICAM-1, VCAM-1, or both. Subsequent to this stable adhesion, leukocytes then transmigrate through the endothelial barrier by an active process involving additional adhesion molecules, retraction of endothelial cells, and chemotactic gradients that attract the cells into the interstitium. The regulated expression of the adhesion molecules involved at various levels of this process is again potentially mediated by various cytokines (interleukin-1, TNFα, IFN-γ) and neuropeptides (substance P, CGRP).

These observations, as well as those reviewed by Salmon and co-workers, clearly demonstrate the essential

role of the skin in immunologic processes. Cutaneous involvement in immune processes occurs at many levels and comprises both cellular and humoral components operating in a complex interplay of signals and responses. Discoveries concerning physiologic properties of the skin immune system have led to important advances in our understanding of both normal and disease events that occur in the skin and other tissues. The overlapping arenas of cell biology, immunology, and directed therapeutics have found fertile ground in the skin and in dermatologic diseases. We can expect that continued advances in the understanding of these processes in both normal and diseased skin will lead to novel therapeutic modalities for a growing number of dermatologic diseases in the coming years.

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Low-Density Lipoprotein Oxidation and the Pathogenesis of Atherosclerosis

THE EPIDEMIOLOGIC ASSOCIATION of low-density lipoprotein (LDL) and coronary heart disease (CHD) has been amply and repeatedly documented. Moreover, clinical trials have clearly demonstrated that clinical manifestations of CHD can be reduced by therapies that reduce LDL-cholesterol levels.[1] Angiographic studies show that the progression of atherosclerotic lesions can be inhibited and lesions can even regress when LDL-cholesterol concentrations are markedly reduced by diet[2] and drug therapy.[3-5] These findings strongly implicate LDL in the pathogenesis of atherosclerosis. But the mechanisms by which LDL damages arterial walls have remained elusive until recently. During the past several years there has been a dramatic increase in our understanding of the mechanisms by which LDL influences the process of atherogenesis. Studies in animals and using human atherosclerotic lesions have provided important insights into the pathogenesis of atherosclerosis in general and about the role of lipoproteins in particular. An important culprit appears to be the oxidation of LDL.

As thoroughly reviewed in the article by Young and Parthasarathy in this issue of the journal,[6] oxidized LDL affects many of the biologic events that occur as atherosclerotic lesions develop and progress. Early studies focused on cellular lipid metabolism, where oxidized LDL has been shown to be taken up by macrophage scavenger receptors and to lead to lipid accumulation, one of the hallmarks of all stages of atherosclerosis. More recent studies have shown that oxidized LDL can be involved in virtually every process of atherosclerosis. Thus, as described in the accompanying article, studies have shown that this modified lipoprotein can stimulate the adhesion of monocytes to endothelial cells and stimulate monocyte chemotaxis, both directly and by inducing the expression of chemotactic factors such as monocyte chemotactic protein 1. T-lymphocyte chemotaxis has recently been shown to be stimulated. These all are early events during the formation of fatty streaks. Oxidized LDL also modulates the expression of growth factors and cytokines that are thought to play a pathogenic role later during atherosclerosis, to influence vascular reactivity, and to stimulate the expression of molecules involved in thrombogenesis, another important component of the atherogenic process.

The observation that several of these events can be influenced by LDL that has undergone only mild oxidative changes is of considerable interest because it suggests that some oxidized lipids formed early during LDL modification can influence gene expression. These pleiotropic effects of oxidized LDL have largely been demonstrated in vitro and have led to the generation of a model whereby the oxidation of LDL plays a central role in the pathogenesis of atherosclerosis.[7,8] In this model, LDL that enters the subendothelial space by transcytosis undergoes mild oxidative changes mediated by endothelial cells. This mildly oxidized form of LDL stimulates the expression of genes such as endothelial adhesion molecules, chemotactic factors and colony-stimulating factors, which result in the attraction, retention, maturation, and activation of monocyte or macrophages and T lymphocytes. With time the LDL becomes more extensively oxidized by macrophages and smooth muscle cells that migrate from the media. Extensively oxidized LDL can lead to macrophage foam cell formation and is cytotoxic. Oxidized LDL also can stimulate the expression of molecules that favor thrombogenesis, which can precipitate clinical events.

Although this model has been generated largely on the basis of experiments performed in vitro, lipoproteins with many of the features of oxidized LDL have been isolated from atherosclerotic lesions.[9] Oxidation-specific epitopes using antibodies generated against oxidized LDL also are present in lesions from both animals and humans.[10,11] Circulating antibodies that recognize oxidized LDL also

have been demonstrated.[11] Thus, there is good evidence for the occurrence of oxidatively modified lipoproteins in vivo. Although several plausible mechanisms for the oxidation of LDL by cells of the artery wall have been described in vitro, the precise mechanism (or mechanisms) by which LDL is oxidized in vivo remains uncertain. Nevertheless, emerging evidence suggests that lipoprotein oxidation may be involved in atherogenesis in several situations associated with increased atherosclerosis risk. These include cigarette smoking,[12] diabetes mellitus,[13] and the atherogenic lipoprotein phenotype that is characterized by the presence of small, dense LDLs.[14] Clinical evaluation of lipoprotein oxidation is difficult because this process is likely to occur in the milieu of the artery wall rather than in the circulation.[15] Thus, investigation of this process in humans has to rely on indirect measures,[15] which are unlikely to be of widespread clinical use.

If lipoprotein oxidation is so important in atherogenesis, then measures that limit this process should be useful in preventing it. As clearly pointed out by Young and Parthasarathy, the role of antioxidants in the prevention of atherosclerosis is supported by several lines of evidence.[6] Perhaps the most convincing evidence comes from studies of animals, where the administration of several antioxidants—probucol, butylated hydroxytoluene, diphenyl phenyldiamene, and vitamin E—has ameliorated the formation of atherosclerotic lesions.[16] Because most of these studies have been done in rabbits, additional data from other atherosclerosis-prone species would be valuable. There also is reasonably strong epidemiologic evidence that the level of consumption of antioxidant vitamins, especially vitamin E, is inversely associated with CHD risk.[17] Two recent large prospective studies suggest that vitamin E protection against the development of CHD is achieved only at doses in excess of those attainable by diet alone.[18,19] Clinical studies also have shown that high doses of vitamin E are required to render circulating LDL relatively resistant to oxidative modification.[20,21] Thus, vitamin supplementation may be the only way that LDL can be protected from oxidative modification. Which vitamins to use, the appropriate doses, and possible side effects remain to be determined.

To date, no placebo-controlled clinical trials have been done using natural antioxidants. The results of a recently completed clinical trial that evaluated the effect of the powerful antioxidant, probucol, on femoral angiographic end points are awaited with interest. Carefully controlled clinical trials of the effect of supplementation with natural antioxidants clearly are needed before their use can be widely recommended in the prevention of CHD. In the meantime, one way of limiting the oxidation of LDL in the artery wall is to keep plasma LDL-cholesterol levels low, a strategy that has been tried and tested and shown to be of benefit.

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Correspondence

California AIDS Drug Assistance Program Expansion

To the Editor: The AIDS Drug Assistance Program by the Department of Health Services, Office of AIDS, has been expanded. This program, funded through a combination of state and federal funds, provides drugs for human immunodeficiency virus (HIV) management to persons without financial means to pay for the drugs. The expansion added one drug, zalcitabine (ddC), on December 1, 1993. Plans call for 12 additional drugs to be added as funds become available: foscarnet sodium, pentamidine (intravenous), amphotericin B, amphotericin with 5FC, acyclovir, rifabutin, paromomycin sulfate, clarithromycin, azithromycin, atovaquone, ethambutol hydrochloride, and clofazimine. These drugs were recommended for addition to the assistance program by an advisory panel to the State Office of AIDS that included community representatives and physicians treating persons with HIV. The 14 medications now available under this program are clindamycin, clotrimazole, dapsone, didanosine, fluconazole, ganciclovir, ketoconazole, nystatin, pentamidine, pyrimethamine, sulfadiazine, the combination drug trimethoprim and sulfamethoxazole, zalcitabine, and zidovudine.

The AIDS Drug Assistance Program is a last resort for those persons with no other resources to pay for treatment. Careful attention is paid to the medications that are provided by the program to assure that they are consistent with current standards of care. To be eligible for the program, a person with HIV or the acquired immunodeficiency syndrome (AIDS) must have a valid prescription from a California-licensed physician and an annual adjusted gross income below $50,000. A co-payment is required for anyone earning more than 400% of the federal poverty level—approximately $27,000.

For more information about the program, the eligibility requirements, and a copy of the program guidelines, please contact Steve Roger, State Department of Health Services, Office of AIDS, PO Box 942732, Sacramento, CA 94234-7320, or at (916) 327-6784.

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Another Wake-up Call

To the Editor: The heart-breaking vignette by Joyce Adams, MD, in the October 1993 issue[1] must have brought tears to the eyes of most readers. Child abuse is a nightmare for any parent, any physician, any caring human being.

I am disturbed, however, by Adams's comment that "Another day was spent in court trying to explain to a judge why an adolescent's examination result would be normal and that her crystal-clear descriptions of abuse should be enough." In the Ingram case, as carefully recorded by Lawrence Wright in his well-researched article, it appears entirely possible that a young woman with malignant intent simply lied about her father (L. Wright, "Remembering Satan," *The New Yorker*, May 17, 1993, pp 60-61 [Pt I]; May 24, 1993, pp 54-75 [Pt II]).

Recently I read Mackay's 1852 description of the hunting of witches.[2] One can extract seven characteristics of a witch hunt:

- A crime of such awfulness that society is highly motivated to take action.
- A willingness to accept a lower order of proof because of that awfulness.
- Dependence on the testimony of children or young women.
- Professionals who assist witnesses to recall events.
- An infusion of sexual or sadistic energy into the process.
- Severe punishments for those convicted.
- Secondary gain for professionals involved.

At the time of the Salem witch trials, young girls who testified had their breasts massaged as an aid to memory. The accused were mostly single women whose property was open to confiscation following conviction. In Europe, torture was used as an inducement to recall.

In many recent cases of alleged child abuse, psychologists have been used to uncover memory. In general, these professionals are in the counseling business, although there is little to suggest that they have profited other than by simply earning a living. Including officers of the criminal justice system, however, many thousands of people are employed in these investigations. Secondary gain for involved professionals might be psychological.

A major difference between the doctors of today and those of the Middle Ages should be that we have a better idea of what constitutes evidence. Child abuse occurs and so does confusion and lying. In some parental abuse cases, we are close to fulfilling the seven criteria of a true witch hunt.

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* * *

Dr Adams Responds

To the Editor: Dr Burdick's response to my essay, "The Wake-up Call,"[1] was both puzzling and disturbing.

I found it curious that Burdick focused on one sentence of the entire essay and seemed to be highly skeptical that an adolescent girl with normal findings on a genital examination could have been molested. He implies that it is dangerous to believe the statements of chil-

dren regarding the details of their abuse because there are occasional cases where a young woman may fabricate totally bizarre allegations of childhood ritual abuse. Burdick seems to be accusing professionals who investigate allegations of abuse, evaluate children, and treat these children as being engaged in a "witch hunt." I would like to try to shed a little light on this topic and refer interested readers to some recent literature reviews.

First of all, although I wrote about a case of a stranger assault that caused definite injury, this was actually not typical of the children referred to our regional evaluation center. We recently reviewed the records of 236 children where the perpetrator was convicted of molesting the child. Only 9% of the children had clear evidence of penetrating genital injury, and 77% had normal or nonspecific findings on examination.[2]

These findings were similar to those reported by De Jong and Rose.[3] In an excellent and comprehensive review of medical findings in suspected child sexual abuse, Bays and Chadwick list eight reasons why an examination of a child victim may be normal, including loss of forensic evidence due to a delay in the examination, rapid healing of injuries, types of abuse that do not involve penetration, elasticity of the hymen and perianal tissues, and incomplete penetration of the vulva (which may still be perceived as penetration by the child).[4]

Are allegations of molestation ever erroneous? Yes, sometimes, but, as stated by Berliner and Conte in their review article, "There is a general consensus that the rate of false allegations in samples of children reporting sexual abuse is quite low."[5(p112)] Most of the allegations that prove to be false are not deliberate fabrications, but arise in families with disturbed psychodynamics; an adult may misinterpret a young child's statement or behavior. The American Professional Society on the Abuse of Children has published guidelines for professionals who examine children with possible sexual abuse, to assist in the objective assessment of the validity of the child's allegation.[6]

The evaluation of suspected sexual abuse is a relatively new field, but we know more now than we did 20 years ago, and the information is being organized into guidelines to assist professionals who have chosen to work in this field. This is difficult work—painful, stressful, and often depressing. To say that professionals receive "secondary gain" from doing abuse work is almost laughable. Few of us are masochists.

I have received several letters of support and encouragement from persons who read my essay, and I thank them for that support. I hope that Burdick will read the articles I have listed here and broaden his understanding of the complex problem of child sexual abuse and its evaluation.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

The Police Officer

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The father sat by the pediatric emergency department entrance, holding his young son securely in his lap. Motionless, as if frozen in stone, the man looked at me with wide, panic-filled eyes that betrayed his outwardly calm appearance. In contrast, the young boy on his lap, feature for feature his father's son, looked around at the semiorganized chaos that is any inner-city pediatric emergency department, his eyes following the people as they raced across in front of him. He fixed his big brown eyes on me as I, having been called over by the triage nurse, approached them.

As the senior resident in the department that night, it was my responsibility to see that the sickest and most severely injured patients be attended to immediately. This child did not look like the usual sick or injured child I would be called to see. He was not unconscious or delirious, nor was he bleeding profusely; he did not have any splints that might indicate a severe fracture. He was in no distress, was breathing comfortably, and had no discernible pain. In short, he looked like a healthy child, being entertained by the circus of motion around him, as any 18-month-old would be.

The child did not cry or jump away as I approached, but rather smiled playfully as he stared at my face, not certain what to make of me. I looked at the nurse with a quizzical smile, trying to understand her urgency to have this child seen right away. She was an excellent nurse, one whose judgment I trusted without question. But it was nearing the end of my shift, and my patience had left me hours ago. As I was about to ask her directly what was so important with this kid, as if she read my mind and sensed my impatience, she nodded silently yet forcefully toward the boy's hand. It was held still on the blanket in which he was wrapped. I had not noticed it as I came near, but now it suddenly struck me. The tip of the right index finger was nearly amputated, hanging on by strands of what appeared to be crushed tendons and ligaments. There was little blood, for the injury had crushed off the blood vessels, in effect sealing them. And there was no pain because the nerves that carry the pain sensation were destroyed as well. There was just gaping pulp of the open wound.

I quickly sprang to action. First I needed to suppress the wave of shock and nausea that swept over me; it would do no one any good if I lost my composure. So, in my well-trained, calm yet firm doctor voice, I managed to say, "Okay, Dad, this is what we need to do." I proceeded to outline the plan of action. We would clean the wound, get x-ray films, and call a plastic surgeon to repair the finger. The father nodded helplessly and followed me, carrying his son.

While we were waiting in the radiology department, I asked the man how the injury had happened. He shook his head with a look of disbelief and recounted the story. The child had been playing with his 4-year-old brother, running around the house, when the older boy accidentally slammed the heavy kitchen door on the younger one's finger. As I smiled the physician's all-knowing smile in an effort to show this man empathy and understanding, he added, "You know, I'm a New York City cop, and I've seen it all. I've taken kids to the hospital with fingers cut off, and a hell of a lot worse. But when it's your own, it's . . . different."

The look in his eyes reflected the deep sincerity of his words, and they hit me hard. They brought my thoughts to my wife, pregnant with our first child, and those words summarized all my fears.

Expecting a first child is a difficult, stress-filled time for everyone, but as a pediatrician, someone who deals only with the sick and the abnormal, it is that much harder. I am terrified of the delivery, but my fears are not those of the usual father-to-be. I know that I will not pass out at the sight of blood or become queasy when things get messy. I carry with me the fear of the hundreds of deliveries that I have attended as a pediatrician, all because something in this natural process has gone awry. At those times I have reacted well, but if the unthinkable occurs and my wife has a problem, will her physicians react appropriately also? I have counseled parents about their gravely ill child's chances without ever fully knowing what weight my words carried. How could I know? How would I react to those words being spoken to me? Just the thought is chilling.

It is not just the catastrophic that paralyzes me with fear; the ordinary is just as scary—4 AM feedings, all-night crying, colic, routine childhood illnesses. I have counseled parents on each of these topics with textbook wisdom, but what will I do when it is my own child? Will each cough be pneumonia, each fever meningitis? And how will I keep my child from all the trouble there is out

(Robin NH: The police officer. West J Med 1994; 160:187-188)

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Reprint requests to Nathaniel H. Robin, MD, Fellow, Division of Human Genetics and Molecular Biology, Rm 5070, Wood Bldg, Children's Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104.

there—the "candy" in the Tylenol bottle, grabbing a hot stove, catching a finger in the kitchen door, or whatever near disasters eager children can get themselves into. It was easy to remain intellectual and calm when it was someone else's child; what will I do when it is mine?

Now I am about to embark on this adventure called fatherhood, both scared and eager. This will be great. I realize now that all I want is what every father wants: a healthy child and the love and wisdom to be a good father. I only hope and pray that when I am faced with whatever adversities occur, I will have the same noble courage that the police officer showed me that night.

A Series of One

WILLIAM R. PHILLIPS, MD, MPH, *Seattle, Washington*

My family practice residency included a training stint in ophthalmology. At first I was surprised at how freely the specialists used chloramphenicol eyedrops for infection and even for prophylaxis. I had been taught to avoid using this drug because of its possibly fatal hematologic complications. On rounds with the eye surgeon, I inquired why ophthalmologists were so willing to expose their patients to these risks. He assured me with the salve of citation: "In the entire world's literature, only one patient has ever been reported to suffer agranulocytosis from chloramphenicol when it was used topically in the eye." Given the enormous number of patients in whom it had been used, he explained, that one case translated into a trivial risk. I accepted the answer, stored it in my cerebral database, and moved on in my training.

My next rotation was infectious diseases at the children's hospital. One of the first patients I admitted was a 5-year-old boy with periorbital cellulitis. Although it was a potentially serious infection, management was straightforward. I treated the boy with intravenous antibiotics to cover *Haemophilus influenzae* and sulfacetamide sodium ophthalmic drops to be given topically. The child was already improving and out of danger by the next morning when I made the rounds with the attending physician.

He was a great professor. He possessed knowledge, wisdom, and compassion. Perhaps because of these, he was an excellent teacher. He taught me how we learn about our patients, our practices, and ourselves. We read studies and quote statistics, but we treat patients. We train on rounds and in the lecture hall, but we practice with people.

The caseload was light that day, and we were searching for some discussion topic with which he might teach some tricks of the trade, if not subtleties of the science. Instead we got wisdom of the world.

Armed with my recently acquired ophthalmologic expertise and the roundsmanship of a senior resident, I brought up the topic of selecting a topical antibiotic for treating eye infections. Although I had already treated the patient with the usual antibiotics, I asked about the appropriateness of using chloramphenicol, particularly in light of its known effectiveness against *H influenzae*.

I knew what the professor's response would be. "We never use chloro, except in cases of life-threatening infections, such as meningitis, and then only if culture and sensitivity or known patterns of drug susceptibility show resistance to first-line antibiotics," he summarized with authority. "The drug is effective but it simply is not worth the risk to the patient," he concluded.

Now was the time to play my part. He had taught us to look to the literature for answers to questions in patient care. He had also once warned us to be wary of physicians who cite their own clinical experience as authority. "We all know about those risks when chloramphenicol is used intravenously or orally," I opened knowingly. "The risk is much lower when used topically in the eye, however," I added. "In fact, there is only one case in the world's literature of a patient who developed hematologic complications from chloramphenicol when it was used as an eyedrop," I explained. I was parroting the answer the ophthalmologist had given me and hoping to sound professional and scientific.

"I know," said the professor. "That patient was mine. He died."

I still study the literature, question unsupported assertions of clinical authority, and try to base my patient care on science. But I never use chloramphenicol eyedrops.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Phillips WR: A series of one. West J Med 1994; 160:188)

Dr Phillips is in private practice in Seattle, Washington.
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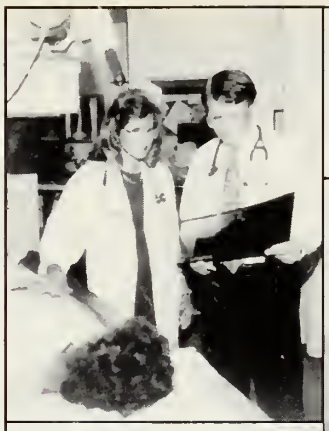

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ATTENTION ADVERTISERS:

The deadline for classified advertising in the **April 1994** issue of WJM is **March 1.**

Call: (415) 882-3376

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PHYSICIANS WANTED

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California Dept. of Industrial Relations
$8,484 per month

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Submit a letter of intent to apply, a curriculum vitae, & two letters of reference, one of which must be from your last employer to:

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Industrial Medical Council
c/o Gayle A. Walsh, D.C.
630 Fountain Ave
Pacific Grove CA 93950

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Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call (800) 873-0786.**

PUGET SOUND. BC/BE Family Practitioners to affiliate with 100 plus physician multispecialty group, located 25 miles north of Seattle. Both walk-in clinic and traditional Family Practice position available. Opportunity for exceptional personal and professional lifestyle. Positions offer competitive salary with excellent benefits. Available immediately. Send CV to J. G. Finley, MD, The Everett Clinic, 3901 Hoyt Ave, Everett, WA 98201.

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ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

(Continued on Page 195)

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(Continued from Page 194)

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(Continued on Page 196)

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at the CMA's Annual Session and Western Scientific Assembly

(Continued from Page 195)

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CARDIOLOGY FIESTA in San Antonio. Update on cardiac diagnostic and therapeutic techniques. April 21-23, 1994. San Antonio, Texas. Fees: $395 for ACC members; $465 for non-members; $250 for fellows-in-training, residents, nurses, physician assistants, and technologists. 17.5 Category 1 credit hours. For information, call American College of Cardiology, (800) 257-4739, FAX (301) 897-9745.

SEVENTH ANNUAL STATE-OF-THE-ART ECHO-CARDIOGRAPHY. February 17-20, 1994. Tucson, Arizona. Fees: $525 for ACC members; $610 for non-members; $415 for fellows-in-training, residents, nurses, physician assistants, and technologists. 24 Category 1 credit hours. For information, call American College of Cardiology, (800) 257-4739; FAX (301) 897-9745.

CONFERENCES

NINTH ANNUAL CARDIOVASCULAR CONFERENCE AT HAWAII. February 14-18, 1994. Hyatt Regency Waikoloa, Kohala Coast, Hawaii. Fees: $450 for ACC members; $545 for non-members; $270 for fellows-in-training, residents, nurses, physician assistants, and technologists. 20.5 Category 1 credit hours. For information, call American College of Cardiology, (800) 257-4739; FAX (301) 897-9745.

CARDIOVASCULAR CONFERENCE AT LAKE LOUISE. February 28-March 3, 1994. Lake Louise, Alberta, Canada. Fees: $410 for ACC members; $495 for non-members; $250 for fellows-in-training, residents, nurses, physician assistants, and technologists. 17.5 Category 1 credit hours. For information, call American College of Cardiology, (800) 257-4739; FAX (301) 897-9745.

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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 18-23, 1994, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 7-11, 1994, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 7-9, 1994, Ritz-Carlton Maunalani, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 28-30, 1994, Sun Valley.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1994, Holiday Inn, Great Falls.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1994, Coronado, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 5-7, 1994, Society Office, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-24, 1994, University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 22-24, 1994, Wenatchee.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 9-11, 1994, Jackson Lake Lodge, Moran.

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Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t1/2) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* [1 hour prior to PRAVACHOL (pravastatin sodium)], *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs. During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/− mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter^2). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General**.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class.

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions. An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interections.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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Bristol-Myers Squibb Company

THE PRAVACHOL® DIRECTION IN LIPID MANAGEMENT

Effective lipid management doesn't have to be tough

- Improves key lipids — significant reduction in LDL-C[1]
- Excellent safety profile
- Easy for patients — once-daily dosing, well tolerated
- Usual dose: 20 mg once daily at bedtime, with or without food

PRAVACHOL®

pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

Bristol-Myers Squibb Company

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Discover The Elegance Of A Hybrid

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A hybrid blending of tolerability and power that's available for the right patient. Vaseretic® is indicated for the treatment of hypertension in patients for whom combination therapy is appropriate.

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VASERETIC® 10-25 *Next*

Enalapril Maleate-Hydrochlorothiazide

Vaseretic® is contraindicated in patients who are hypersensitive to any component of this product or to other sulfonamide-derived drugs and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Dosage must be individualized; the fixed combination is not for initial therapy. **Evaluation of the hypertensive patient should always include assessment of renal function.** For a Brief Summary of Prescribing Information, see adjacent pages.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General; Enalapril Maleate; Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions,* and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy, Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality,* below.)

Enalapril Maleate; Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

10 mg

25 mg

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats, and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide; Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General; Enalapril Maleate; Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions.*)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients; Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension. Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure, patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions; Enalapril Maleate; Hypotension—Patients on Diuretic Therapy. Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium. Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution

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assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse bone marrow assay.
Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.
Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.
Pregnancy, Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*
Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*
Clinical Laboratory Test Findings, Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.
Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide—Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

For more detailed information, consult your DuPont Pharma Representative or see Prescribing Information.

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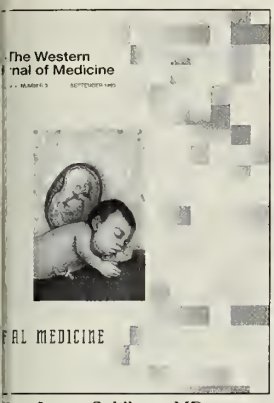

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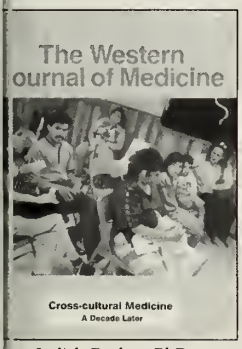

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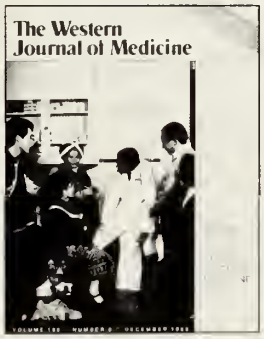

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Thursday: 12:00 pm to 7:00 pm; Friday, Saturday, and Sunday: 7:00 am to 5:00 pm

For a copy of the Advance Program or other information about Annual Session events, call Western Scientific Assembly at (415) 882-3384.

ABSTRACTS MARCH 1994

(Claman HN, Robertson AD: Antinuclear antibodies and breast implants. West J Med 1994; 160:225-228)

Anecdotal reports have linked silicone breast implants to autoimmune diseases, with scleroderma being mentioned most often. In view of other environmental influences—such as silica mining and the toxic oil syndrome—thought to predispose to scleroderma, more systematic immunologic information on women with silicone implants is needed to assess any possible relation to autoimmunity.

A cross-sectional survey was carried out with 150 women, of whom 131 had implants. Group 0 consisted of 19 volunteer women without breast implants who felt healthy, group I was 38 volunteer women with breast implants who felt healthy, group II was 82 women with implants who had various symptoms, and group III was 11 women with implants who had autoimmune disease. Scleroderma was overrepresented in group III (6 of 11). Antinuclear antibodies were determined on Hep-2 cells, using serum dilutions of 1:16, 1:64, and 1:256. A positive test was indicated by 1+ or more fluorescence at 1:256. Antinuclear antibody tests were positive in 0% of group 0, 18% of group I ($P < .05$ versus group 0), 26% of group II, and 64% of group III. There was no correlation between antinuclear antibody positivity and type of implant, indication for implantation, time since first implantation, total number of implants, and report of implant leak or rupture.

Women with breast implants may be at risk for the development of antinuclear antibodies. Proof of such an association will require large-scale prospective studies and epidemiologic analyses.

BREAST IMPLANTS **SCLERODERMA**
ANTINUCLEAR ANTIBODIES

(Claman HN, Robertson AD: Antinuclear antibodies and breast implants. West J Med 1994; 160:225-228)

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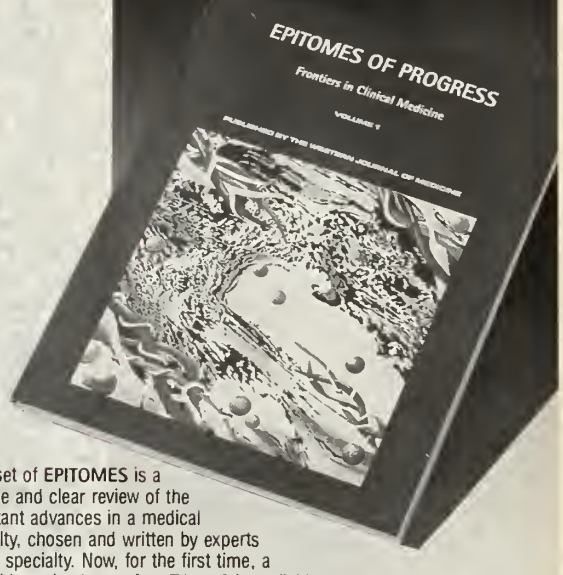

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

March 17-19—**21st Annual Symposium: Recent Advances in Neurology and Neurosurgery.** St Joseph's Hospital and Medical Center at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Beverly Pennington, (602) 285-3067.

March 18-20—**18th Annual James H. McDonald Urological Seminar.** Maricopa Medical Center at Scottsdale Plaza Resort. Fri-Sun. Contact: (602) 267-5366.

March 24-26—**Third Annual Urogynecology and Disorders of the Female Pelvic Floor.** Mayo Clinic-Scottsdale at The Pointe Hilton, Tapitio Cliffs. Thurs-Sat. Contact: Tamara Zelinski, (602) 301-7447.

March 27-30—**Management Strategies in Complex Congenital Heart Disease.** Mayo Foundation-Rochester at Scottsdale Princess Resort, Scottsdale. Sun-Wed. Contact: (800) 323-2688.

April 6-9—**Nineteenth Annual Primary Care Update.** University of Arizona College of Medicine at Hilton East, Tucson. Wed-Sat. Contact: U of A.

April 7-9—**Advanced Arthroscopic Surgery.** American Academy of Orthopedic Surgeons at The Pointe Hilton Resort, Squaw Peak, Phoenix. Thurs-Sat. Contact: AAOS, (708) 823-7186.

April 14-15—**Update on New Drugs.** University Learning Systems, Scottsdale. Thurs-Fri. Contact: (800) 940-5680.

April 14-16—**National Conference on Skin Cancer.** American Cancer Society at Crescent Hotel, Koll Center, Phoenix. Thurs-Sat. Contact: (404) 329-7604.

April 15-17—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Camelback Inn, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

April 18-23—**1994 Annual Meeting—Osteopathic Medical Association.** Wyndham Paradise Valley Resort, Scottsdale. Mon-Sat. Contact: (602) 840-0460.

April 29-30—**Twenty-sixth Annual Pediatric Orthopedic Symposium.** Maricopa Medical Center. Fri-Sat. Contact: Beverly Anderson, (602) 267-5366.

May 4-6—**Practice Parameters and Guidelines: Impact on Quality.** American Board of Quality Assurance and Utilization Review Physicians at the Arizona Biltmore, Phoenix. Wed-Fri. Contact: (813) 286-4411.

May 13—**Pediatric Advanced Life Support: Recertification Course.** Phoenix Children's Hospital at Good Samaritan Regional Medical Center. Fri. Contact: (602) 239-3563.

May 14—**Topics in Head and Neck Reconstruction.** Mayo Clinic-Scottsdale at the Ashton B. Taylor Auditorium, Scottsdale. Sat. Contact: Tamara Zelinski, (602) 301-7447.

May 14-17—**1994 Annual Meeting—American Pediatric Surgical Association.** Loews Vantana Canyon Resort, Tucson. Sat-Mon. Contact: (816) 234-3579.

May 21—**Current Topics in Head and Neck Reconstruction.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Scottsdale. Sat. Contact: Tamara Zelinski, (602) 301-7447.

June 2-4—**Arizona Medical Association Annual Meeting.** Scottsdale Plaza Resort. Thurs-Sat. Contact: ArMA.

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ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

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ALLERGY/IMMUNOLOGY

March 19—**Immunologic Controversies Facing the Private Practitioner.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Strott, (415) 882-3384.

ANESTHESIOLOGY

March 19-20—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort. Sat-Sun. 9 hrs. $185. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

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CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
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UCLA: University of California, Los Angeles Extension
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UCSF: University of California, San Francisco
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USC: University of Southern California
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CONTINUING MEDICAL EDUCATION

(Continued from Page 210)

April 2-3—**22nd Obstetric/Anesthesia Conference.** Ohio State Department of Anesthesiology at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Sun. 20 hrs. $610. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

April 5-8—**Hawaiian Pain Conference.** Ohio State University Department of Anesthesiology at Grand Hyatt, Wailea, Maui. Tues-Fri. 16 hrs. $610. Contact: Arlene Rogers, Ohio State University, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8153.

April 9-10—**39th PGA Conference.** Los Angeles County Society of Anesthesiologists at UCLA Faculty Center. Sat-Sun. 13 hrs. Contact: LACSA, PO Box 90999, Long Beach 90809-0999. (213) 597-2661.

May 19-22—**California Society of Anesthesiologists Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $225-$325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

May 22-27—**Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun-Fri. 45 hrs. $500. Contact: UCSD.

CARDIOLOGY

March 25-26—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at MGM Grand, Las Vegas, Nevada. Fri-Sat. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

April 11-13—**4th Annual Symposium on Coronary Stenting.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 13-15—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Doubletree Resort, Palm Springs. Fri-Sun. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

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For more information and application for registration, contact course coordinators:

Alan Barkin, MD
Internal Medicine
Permanente Medical Group
1150 Veterans Blvd.
Redwood City, CA 94063
(415) 299-2508
FAX (415) 299-3066

or Eric Tepper, MD
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1994 SPRING/SUMMER SERIES HIGHLIGHTS

APRIL 1994

1. Obstetrics-Gynecology Clinical Update
   April 29-May 1, 1994 Denver, CO

MAY 1994

2. Obstetrical Ultrasound
   May 12-15, 1994 Denver, CO
3. 22nd Annual Child Abuse and Neglect Symposium
   May 23-27, 1994 Keystone, CO

JUNE 1994

4. 40th Annual Family Practice Review
   June 12-18, 1994 Estes Park, CO
5. 7th World Conference on Lung Cancer
   June 26-July 1, 1994 Colorado Springs, CO

JULY 1994

6. Integrative Care of Head and Neck Cancer Patients
   July 1, 1994 Denver, CO
7. Treating the Hypoxic Patient
   July 5-9, 1994 Snowmass, CO
8. 30th Annual Internal Medicine Program
   July 10-15, 1994 Estes Park, CO
9. 21st Annual Renal Disease Program
   July 25-29, 1994 Aspen, CO
10. Cardiovascular Intervention: Technology at the Summit, IV
    July 21-August 3, 1994 Aspen, CO
11. 3rd Biannual Type I Diabetes Program
    July 31-August 3, 1994 Keystone, CO

AUGUST 1994

12. 18th Annual Dynamic Psychotherapy Program
    August 1-5, 1994 Aspen, CO
13. 37th Annual Pediatric Program
    August 7-11, 1994 Aspen, CO
14. 19th Annual Primary Musculoskeletal Care
    August 7-12, 1994 Breckenridge, CO
15. The Failing Pediatric Heart
    August 11-14, 1994 Aspen, CO
16. Breast Imaging and Intervention
    August 15-19, 1994 Colorado Springs, CO
17. 4th Annual Musculoskeletal Infection Course
    August 18-20, 1994 Snowmass, CO

SEPTEMBER 1994

18. The Changing Colors of Outreach Education
    September 16-18, 1994 Durango, CO
19. 3rd Annual Medical Ethics Conference
    September 16-18, 1994 Aspen, CO
20. Rocky Mountain Regional Cardiovascular Disease Conference
    September 30, 1994 Vail, CO

NOVEMBER 1994

21. 40th Annual Family Practice Review
    November 7-11, 1994 Denver, CO

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252 **Tuberculosis and Human Immunodeficiency Virus Disease**
LAURENCE PEIPERL, MD, and MERLE A. SANDE, MD

253 **Hormonal Therapy for Metastatic Prostate Cancer**
ERIC J. SMALL, MD

254 **Current Diagnosis and Treatment of *Helicobacter pylori***
ADEL YOUSSEF, MD, and YANG K. CHEN, MD

255 **Heparin Therapy for Venous Thromboembolism**
DAVID J. TANAKA, MD

ALERTS, NOTICES, AND CASE REPORTS

257 **Acute Histoplasmosis Acquired in Mexico**
CARL M. KIRSCH, MD; WILLIAM A. JENSEN, MD; FRANK T. KAGAWA, MD; and ANTHONY C. CAMPAGNA, MD
From the Division of Respiratory and Critical Care Medicine, Santa Clara Valley Medical Center, San Jose, California.

259 **Factitious Simulation of Systemic Lupus Erythematosus**
JONATHAN D. APFELBAUM and H. JAMES WILLIAMS, MD
From the Department of Internal Medicine, Division of Rheumatology, University of Utah School of Medicine, Salt Lake City.

261 **Black Widow Spider *(Latrodectus mactans)* Bite During Pregnancy**
CHERYL C. HANDEL, MD; LUIS Z. IZQUIERDO, MD; and LUIS B. CURET, MD
From the Regional Academic Health Center, Texas Tech University School of Medicine, El Paso, and the Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, University of New Mexico School of Medicine, Albuquerque. Dr Handel is now with the Department of Obstetrics and Gynecology, University of Oklahoma College of Medicine, Oklahoma City.

SPECIAL SERIES

263 **A Brief History of Health Care Quality Assessment and Improvement in the United States**
JOHN M. LUCE, MD; ANDREW B. BINDMAN, MD; and PHILIP R. LEE, MD
From the Department of Medicine and the Institute for Health Policy Studies, University of California, San Francisco, School of Medicine, and the Department of Medicine and the Department of Quality Assessment and Improvement, San Francisco General Hospital Medical Center. Dr Lee is now the Assistant Secretary for Health, US Department of Health and Human Services, Washington, DC.

COMMENTARY

269 **Will Managed Care Alter the Art and Soul of Medicine?**
MARVIN L. AUERBACK, MD
From the Foster City Pediatric Medical Group, Foster City, California.

Responses

270 **Defending the Art**
CLIFTON R. CLEAVELAND, MD
From the Department of Medicine, University of Tennessee School of Medicine, Chattanooga.

271 **Physicians' Responsibility Under Health Care Reform**
BRUCE SAMS, MD
Dr Sams is in private practice in Belvedere, California.

271 **Who Will Manage Patient Care?**
ROBERT C. CHARMAN, MD
From Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.

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CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

APRIL 7-10 1994

FOCUS ON THE FEMALE PATIENT
LOCATION: Howey-in-the-Hills (Orlando), Florida
SPECIALTY: Primary Care, Ob/Gyn
CME CREDIT: AMA Category I
FEE: SMA Member $310; Nonmember $435

APRIL 15-17, 1994

ADDICTION MEDICINE
LOCATION: New Orleans, Louisiana
SPECIALTY: Primary Care, Psychiatry, Emergency Medicine
CME CREDIT: AMA Category I, 15 hours
FEE: SMA Member $350; Nonmember $475

APRIL 15-17, 1994

ORTHOPAEDIC UPDATE
LOCATION: Wrightsville Beach, NC
SPECIALTY: Orthopaedic Surgery
CME CREDIT: AMA Category I, 14 hours
FEE: SOA Member $125; SMA Member $225; Nonmember $350

APRIL 22-24, 1994

INFECTIOUS DISEASES
LOCATION: Atlanta, Georgia
SPECIALTY: Primary Care
CME CREDIT: AMA Category I, 15 hours
FEE: SMA Member $310; Nonmember $435

MAY 20-22, 1994

DIAGNOSTIC TECHNIQUES
LOCATION: Atlanta, Georgia
SPECIALTY: Primary Care
CME CREDIT: AMA Category I
FEE: SMA Member $310; Nonmember $435; Nonphysician $225

MAY 20-22, 1994

CURRENT CONCEPTS IN ORTHOPAEDICS
LOCATION: Baltimore, Maryland
SPECIALTY: Orthopaedic Surgery
CME CREDIT: AMA Category I,
FEE: SOA Member $175; SMA Member $275; Nonmember $400; Resident or Fellow $50; Nonphysician $75

JUNE 9-11, 1994

SOUTHERN ASSOCIATION FOR GERIATRIC MEDICINE, FOURTH ANNUAL MEETING
LOCATION: Hilton Head, South Carolina
SPECIALTY: Geriatrics
CME CREDIT: AMA Category I
FEE: To be announced

JUNE 12-16, 1994

EIGHTEENTH SYMPOSIUM ON LUNG DISEASE
LOCATION: Sea Island, Georgia
SPECIALTY: Pulmonary and Critical Care Medicine
CME CREDIT: AMA Category I, 22 hours
FEE: SMA/Southern ACCP Member $415; Nonmember $540; Nonphysician $275

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!

(Continued from Page 211)

June 3-5—**Pediatric Electrophysiology, Pacing Course and Board Review.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. $425. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

July 22-24—**Coronary Heart Disease.** American College of Emergency Physicians at Marriott Tenaya, Yosemite. Fri-Sun. 11 hrs. Contact: Karen DeBont, Meetings Coordinator, 1500 W Canal Ct, Ste #500, Littleton, CO 80120-4528. (800) 421-3756.

July 24-28—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 19 hrs. Contact: UCD.

DERMATOLOGY

March 18—**Current Issues in Dermatology.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

July 19-23—**11th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD and Scripps Clinic at La Jolla. Tues-Sat. 33 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037 (619) 554-8556.

EMERGENCY MEDICINE

March 14-18—**Emergency Medicine Symposium II.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

March 23-27—**Winter Wilderness Medicine: 1994.** American College of Emergency Physicians at Squaw Valley (Lake Tahoe). Wed-Sun. 21 hrs. $450. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 888-5632.

April 6-9—**Advances in Emergency Medicine.** UCSF at Stouffer's Stanford Court Hotel, San Francisco. Wed-Sat. 22 hrs. $465. Contact: UCSF.

May 9-13—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 20-24—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

August 15-19—**Emergency Medicine Symposium II.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

ENDOCRINOLOGY/METABOLISM

March 17—**Diabetes Update: 1994.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs. 6.5 hrs. $185. Contact: UCSF.

March 18-19—**Advances in Endocrinology and Metaholism.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sat. 11.5 hrs. $295. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

March 18—**Cancer Detection and Follow-Up for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 19—**Emergencies in Primary Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 19—**Psychiatric Emergencies in Primary Care: A How To Primer.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20—**Outpatient Procedures for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20—**Urology for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 5.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 23-25—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $300. Contact: UCSF.

March 28-31—**Primary Care in Paradise.** Scripps Clinic and Research Foundation at Princeville Resort, Island of Kauai, Hawaii. Mon-Thurs. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

April 3-8—**Primary Care Medicine 1994.** UCSF at Maui Intercontinental Resort. Sun-Fri. 20.5 hrs. $545. Contact: UCSF.

April 21-24—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

May 5-7—**Primary Care for the '90s.** University of Nevada School of Medicine at Resort at Squaw Creek, Olympic Valley. Thurs-Sat. 15.5 hrs. $260-$290. Contact: University of Nevada, Manville Bldg/342, Reno, NV 89557. (702) 784-4605.

May 11-14—**16th Semi-Annual Wound Management for Primary Care Health Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $250-$475. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

May 13-14—**Coming of Age: Geriatrics for Primary Care Providers–Part I.** UCD at Sacramento. Fri-Sat. Contact: UCD.

May 31-June 4—**21st Annual UCLA Family Practice Refresher Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Tues-Sat. 32 hrs. $485. Contact: UCLA.

June 12-17—**18th Annual Fingers to the Toes Orthopaedics for Primary Care.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. 25 hrs. Contact: UCD.

June 23-26—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 18 hrs. $370. Contact: UCLA.

July 5-7—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Tues-Thurs. 20 hrs. $350. Contact: UCSF.

1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

March 17-18—**Alzheimer's Disease Conference.** Advances in Treatment 1994. UCSD at Pan Pacific Hotel, San Diego. Thurs-Fri. 16 hrs. $195. Contact: UCSD.

March 20—**Long Term Care Update.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 30—**Caring for the Older Female Patient.** UCSF and Mount Zion Center on Aging at Miyako Hotel, San Francisco. Sat. Contact: Mount Zion Institute on Aging, (415) 750-4170.

May 13-14—**Coming of Age: Geriatrics for the Primary Care Provider—Part I.** UCD at Sacramento Inn. Fri-Sat. 13 hrs. Contact: UCD.

June 4—**Heart Disease in the Elderly.** UCSF and Mount Zion Center on Aging at Miyako Hotel, San Francisco. Sat. Contact: Mount Zion Institute on Aging, (415) 750-4170.

1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

INTERNAL MEDICINE

March 17-19—**Infectious Diseases in Clinical Practice.** UCSF at Squaw Valley, North Lake Tahoe. Thurs-Sat. 12 hrs. $335. Contact: UCSF.

March 18-20—**Current Issues in Blood Substitute Research and Development.** UCSD at Hyatt Regency San Diego on the Bay. Fri-Sun. 18 hrs. $600. Contact: UCSD.

March 18-24—**Internal Medicine: 1994.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Thurs. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 17-19—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. 12 hrs. Contact: Karen Debont, 1500 W Canal Crt, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

July 9-16—**3rd National Kaiser Permanente Internal Medicine Conference.** Permanente Medical Group at Ritz-Carlton Hotel, Kapalua, Maui, Hawaii. 1 wk. 22 hrs. Contact: Eric Tepper, MD, 3400 Delta Fair Blvd, Antioch 94509. (510) 779-5211.

OB/GYN

March 19—**Health Care Issues for Women Over 40.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

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April 20-24—**Pacific Coast Fertility Society Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 17 hrs. Contact: Director, Continuing Medical Education, 15731 Imperial Hwy, Ste 427, La Mirada 90638-2510. (310) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

March 19—**Practical Aspects of Occupational Medicine.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

June 3-4—**Occupational and Environmental Medicine.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

July 25-29—**8th Annual Sports Medicine.** UCSD at San Diego Princess Resort. Mon-Fri. 20 hrs. $395. Contact: UCSD.

ONCOLOGY

April 30—**Cancer in Women: Management of Breast and Gynecologic Malignancies.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

July 19-22—**Pan Pacific Lymphoma Conference.** University of Nebraska Medical Center at Ritz-Carlton-Mauna Lani, Kohala Coast, Hawaii. Tues-Fri. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

OPHTHALMOLOGY

March 20—**Ophthalmologist-Gatekeeper Interactions: Managed Eye Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 25-27—**Ophthalmology.** Research Study Club of Los Angeles at Huntington Ritz Carlton Hotel, Pasadena. Fri-Sun. 15 hrs. $425. Contact: Louise Ball, PO Box 1216, Murrieta, CA 92564. (909) 677-4482.

May 21—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

ORTHOPEDICS

March 20—**Musculoskeletal Trauma in Children and Adolescents.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

May 19-21—**Fractures of the Shoulder and Elbow.** American Academy of Orthopaedic Surgeons at San Diego Marriott Hotel and Marina. Thurs-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

May 20-21—**New Techniques and Technologies in Total Hip Replacement.** American Academy of Orthopaedic Surgeons at Sheraton Palace Hotel, San Francisco. Fri-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

July 8-9—**Spine and Strength Symposium.** UCSD at Marriott, La Jolla. Fri-Sat. $300. Contact: Kerri Kazala, 4150 Regents Park Row #300, La Jolla 92037. (619) 625-0026.

1994—**Educational Program for Musculoskeletal Evaluation and Rehabilitation.** UCSD at La Jolla. 35.5 hrs. $500. Contact: UCSD.

OTOLARYNGOLOGY

March 13-18 and April 10-15—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

March 18—**Pediatric Otolaryngology: What Gatekeepers Need to Know.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 25-27—**Otolaryngology.** Research Study Club of Los Angeles at Huntington Ritz Carlton Hotel, Pasadena. Fri-Sun. 15 hrs. $425. Contact: Louise Ball, PO Box 1216, Murrieta, CA 92564. (909) 677-4482.

April 6-8—**Temporomandibular Joint Update.** UCD at Silverado Resort, Napa. Wed-Fri. 12 hrs. $325. Contact: UCD.

PATHOLOGY

March 18—**Skin Cancer: A Clinical and Histopathologic Update.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

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April 16—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Fri. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

May 26-28—**10th Annual Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

PEDIATRICS

March 19—**Pediatrics Emergencies.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 7-10—**Pediatrics in Yosemite.** Valley Children's Hospital. Thurs-Sun. 10.25 hrs. $370. Contact: Valley Children's Hospitals, 3151 North Millbrook, Fresno 93703. (209) 225-3000.

April 15-16—**Pediatric Dermatology for the Practitioner.** Children's Hospital and Health Center at L'Auberge Del Mar Hotel, San Diego. Fri-Sat. 12 hrs. $245. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

May 12-14—**27th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

June 1-3—**13th Annual Child Abuse and Neglect Conference.** UCD at Radisson Hotel, Sacramento. Wed-Fri. Contact: UCD.

June 3-5—**Pediatric Electrophysiology, Pacing Course and Board Review.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. $425. Contact: Children's Hospital, 30202 Children's Way, San Diego 92123. (619) 576-4072.

June 24-26—**Current Concepts in Child Neurology 1994.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15 hrs. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

July 15-17—**2nd Annual Pediatric Update.** Stanford University School of Medicine at Lucile Packard Children's Hospital, Palo Alto. Fri-Sun. Contact: Elinor Meyer, Medical Outreach Dept, 725 Welch Rd, Palo Alto 94304. (415) 497-8554.

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JOHN F. BURNUM, MD
Dr Burnum is in private practice in Tuscaloosa, Alabama.

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WILLIAM B. STEWART, MD
From the Program in Medicine and Philosophy, California Pacific Medical Center, San Francisco.

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CHARLES B. HIGGINS, MD
Dr Higgins is Chief, MRI Section, Department of Radiology, University of California, San Francisco, School of Medicine.

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FERRIS M. HALL, MD
From the Department of Radiology, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts.

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BARRY L. ROTMAN, MD
From the Section of General Internal Medicine, Department of Veterans Affairs Medical Center, Palo Alto, California.

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Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of YOCON® 1/12 gr. 5.4mg in bottles of 100's NDC 53159-001-01, 1000's NDC 53159-001-10 and Blister-Paks of 30's NDC 53159-001-30

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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PROGRAM PROFILE

USC Center For Colorectal Diseases

A CASE STUDY

A 37-year-old male presented with a 17 year history of ulcerative colitis. On rectal exam, a 2 cm. polyp on a stalk was noted and removed. It contained an invasive carcinoma. Surgical judgments and alternatives for the management of this problem are complex.

Current understanding on the margins of resection, use of adjuvant therapy, and the technical issues of continence preservation, interplay in this complex case. Recognition of the appropriate use of nerve sparing rectal dissection with wide lymphadenectomy allowed for an adequate cancer procedure while preserving the sphincter mechanism. A compliant and capacious pouch was created and intestinal continuity was restored.

The patient has recovered, retained his sexual potency and maintained fecal continence with five bowel movements a day. He is fully active and continues long distance running as a hobby.

The USC Center for Colorectal Diseases is a university-based private practice that offers the full range of advanced diagnostic and treatment alternatives for patients with colorectal disease and fecal incontinence. Offering advanced expertise in a university setting, the Center provides primary *and* tertiary management of colorectal disease, including inflammatory bowel disease, ulcerative colitis and Crohn's disease. It conducts sophisticated physiological tests to evaluate anorectal physiology in patients who have difficulty with fecal incontinence.

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Innovative Surgical Alternatives

The Center's specialists have expertise in the surgical alternatives to ileostomy and colostomy, including:

- Koch Pouch: This continent intestinal reservoir allows patients to store waste and control its discharge after coloproctectomy, thus eliminating the need for an external appliance.
- Ileal Pouch-Anal Anastomosis: In this procedure, surgeons create a pouch out of the terminal ilium and sew it to the anal muscles, and perform a temporary ileostomy. Six to eight weeks later, they close the ileostomy, and patients can defecate normally.
- Laparoscopically Assisted Colectomy: Surgeons can now effectively remove segments of the colon through this minimally invasive technique.

The Center's comprehensive services include:

- Colonoscopy
- Management of recurrent colorectal cancer
- Anorectal physiologic studies
- Evaluation of continence disorders
- Continence preserving and restoring surgical procedures
- Post-operative pain management, rehabilitation and education
- Research activities including the physiology of continence and surgical techniques
- Educational activities to support physicians in the development of current surgical techniques

Center surgeons perform all major surgeries at USC University Hospital or USC/Norris Cancer Center. Both facilities provide the latest in technology, patient care and dedicated colorectal trained nurses.

Physician Support and Education

As an academically based program, the Center is dedicated to providing continuing education and support for physicians practicing in the community setting. Physicians are encouraged to contact USC PACE for patient consultation or program information.

About the Director

Robert W. Beart, Jr., M.D., *Professor of Surgery at the USC School of Medicine, serves as Director of the USC Center for Colorectal Diseases. He is a world-renowned specialist in colon and rectal surgery, with extensive experience in performing and refining surgical alternatives to ileostomy and colostomy and laparoscopic colon resection.*

Dr. Beart received his medical degree from Harvard Medical School, and completed his internship and residencies at the University of Colorado Medical Center in Denver. He did a transplant fellowship (liver and kidney) at the University of Colorado, and a colon and rectal fellowship at the Mayo Clinic Rochester. For more than a decade, he served as Chairman, Colon and Rectal Surgery at the Mayo Clinic Rochester, and was named the Caywood Professor of Surgery. At the Mayo Clinic Scottsdale (Arizona), he was Chairman, Department of General Surgery. He joined USC University Hospital in 1992.

Dr. Beart, a member of numerous professional organizations, is the immediate Past President of the American Society of Colon and Rectal Surgeons. He is widely published in peer review journals, is the editor of Diseases of the Colon & Rectum, *and is a much sought after lecturer.*

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(Continued from Page 215)

PSYCHIATRY

April 8-9—**West Coast Neuropsychology Conference: Part I.** UCSD at Pan Pacific Hotel, San Diego. Fri-Sat. 9 hrs. $175. Contact: UCSD.

April 9-11—**West Coast Neuropsychology Conference: Part II.** UCSD at Pan Pacific Hotel, San Diego. Sat-Mon. 14 hrs. $325. Contact: UCSD.

April 22-26—**The Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Colonial Inn, La Jolla. Fri-Tues. 26 hrs. $550. Contact: UCSD.

April 30-May 1—**Self Psychological Revolution: Psychotherapy Since Kohut.** UCSD at Pan Pacific Hotel, San Diego. Sat-Sun. 13 hrs. $325. Contact: UCSD.

June 28-July 3—**Neuropsychiatric Aspects of Aging: Update and Review.** Southern California Neuropsychiatric Institute at Mauna Kea Hotel, Hawaii. Tues-Sun. 22 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

1994—**Basic Clinical Hypnosis Training.** UCSD at La Jolla. Ongoing. 30 hrs. $245. Contact: UCSD.

RADIOLOGY

March 19—**Dilemmas in Women's Imaging.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20-25—**UCLA General Radiology Review Course.** UCLA at Doubletree Hotel, Marina Del Rey. Sun-Fri. 40 hrs. $420. Contact: UCLA.

March 21-26—**Musculoskeletal and Neuro MRI.** UCSD at La Costa Resort and Health Spa, Carlsbad. Mon-Sat. 19.5 hrs. $550. Contact: UCSD.

April 3-8—**14th Annual Residents Radiology Review Course.** UCSD at Hotel Del Coronado, San Diego. Sun-Fri. 41 hrs. $450. Contact: UCSD.

April 9—**Interventional Radiology.** UCSD at Hotel Del Coronado, San Diego. Sat. 8 hrs. $135. Contact: UCSD.

April 17-22—**Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: UCSD.

1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

1994—**Visiting Fellowship Program of Endovaginal Sonography: Focus on Techniques and Application.** UCSD Medical Center. Monthly. 30 hrs. $600. Contact: UCSD.

SURGERY

March 24-25—**9th Annual Course in Colon and Rectal Surgery.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Thurs-Fri. Contact: Donna Bowker, 1975 Zonal Ave, KAM 307, Los Angeles 90033. (213) 342-2555.

March 24-26—**6th Annual Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

June 23-25—**20th Annual Meeting of the Western Thoracic Surgical Association.** WTSA at Resort at Squaw Creek, Olympic Valley. Thurs-Sat. Contact: WTSA, (508) 526-8330.

GENERAL/MULTIDISCIPLINARY

March 18-19—**Healthcare in Transition.** California Pacific Medical Center at San Francisco. Fri-Sat. Contact: Laura Johnson, (415) 923-3242.

March 20—**Risk Issues in Cost Contained Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 25-27—**63rd Clinical Conference.** Research Study Club at Huntington Ritz-Carlton Hotel, Pasadena. Fri-Sun. 15 hrs. Contact: Louise Ball, PO Box 1216, Murrieta 92564. (909) 677-4482.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

March 19-26—**Cancer Treatment Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 20-23—**Colorado Conference on Decision-Based Family Practice.** University of Colorado Health Sciences Center, Denver. Sun-Wed. Contact: U of Colo.

April 8-10—**Urogynecology: Urogenital Health in Adult Women.** P/SL Swedish Healthcare System at Beaver Run Resort, Breckenridge. Fri-Sun. Contact: Mary Fletcher, (800) 633-6824.

April 16—**Born Too Soon: Perinatal Conference.** P/SL Swedish Healthcare System at Presbyterian/St Luke's Medical Center, Denver. Sat. Contact: Mary Fletcher, (800) 633-6824.

June 12-18—**40th Annual Family Practice Review.** University of Colorado Health Sciences Center at YMCA of the Rockies, Estes Park. Sun-Sat. Contact: U of Colo.

July 8-10—**Common Problems in Primary Care.** P/SL Swedish Healthcare System at Snowmass. Fri-Sun. Contact: Nancy Manuel, (303) 788-6209.

July 8-10—**Current Concepts in Heart Failure: Medical Treatment to Mechanical Support and Transplantation.** P/SL Swedish Healthcare System at Snowmass. Fri-Sun. Contact: Nancy Manuel, (303) 788-6209 or P/SL CME Office, (800) 633-6824.

August 1-5—**Dynamic Psychotherapy Program.** University of Colorado Health Sciences Center at Aspen. Mon-Fri. Contact: U of Colo.

August 7-12—**19th Annual Primary Musculoskeletal Care Program.** University of Colorado Health Sciences Center at Breckenridge. Sun-Fri. Contact: U of Colo.

August 11-14—**Multimodality Approaches to Limb Salvage for Extremity Sarcoma.** P/SL Swedish Healthcare System at Westin Resort, Vail. Thurs-Sun. Contact: P/SL CME Office, (800) 633-6824.

August 15-20—**Breast Imaging and Intervention Into the 21st Century.** Radiology Imaging Associates at Broadmoor Hotel, Colorado Springs. Sun-Fri. Contact: Ryals & Associates, (404) 641-9773.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

Every Friday (except 4th Friday of month)—**Various Topics in Contemporary Medicine (Midday CME Series).** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

May 5-7—**Idaho Academy of Family Physicians 46th Annual Meeting.** Coeur d'Alene Resort, Coeur d'Alene. Thurs-Sat. Contact: Irma Sparks, Executive Director, Idaho Academy of Family Physicians, 777 N Raymond, Ste 100, Boise 83704. (208) 323-1156.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 220)

July 28-30—**Idaho Medical Association—Annual Meeting.** Sun Valley. Wed-Fri. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 26—**Vascular Update.** Savage Auditorium, Presbyterian Hospital, Albuquerque. Contact: Mary R. Boning, Presbyterian Healthcare Services, (505) 841-1225.

April 22-23—**James Wiggins, MD, Lectureship.** Albuquerque Convention Center. Contact: Mary R. Boning, Presbyterian Healthcare Services, (505) 841-1225.

May 6-7—**New Mexico Medical Society Annual Meeting.** The Marshall Building, Albuquerque. Fri-Sat. Contact: Elsa Hall, 7770 Jefferson NE, Suite 400, Albuquerque 87109, (505) 828-0237.

July 18-22—**Imaging 1994.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925, (404) 641-9773.

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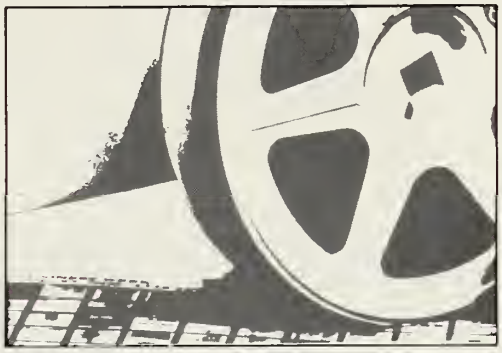

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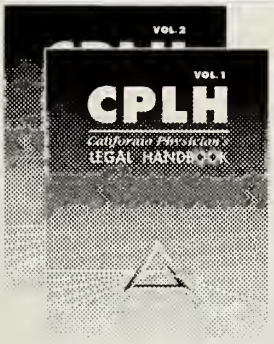

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(Continued from Page 221)

August 7-11—**Lovelace Santa Fe Neurology 1994.** Eldorado Hotel, Santa Fe. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

March 30—**Medical Ethics and Health Care Reform: New Issues on the Table.** Division of Medical Ethics, LDSH, UUMC. 7.5 hrs. $75. Contact: LDSH, Division of Medical Ethics, (801) 321-1135.

May 18-20—**Odgen Surgical-Medical Annual Meeting.** Ogden Park Hotel, Ogden. Wed-Fri. 21 hrs. Contact: KayLynne, (801) 625-3122.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

March 24-25—**Office Management of Chronic Pain.** Seattle. Thurs-Fri. Contact: U/W.

March 25—**Arthrogryposis and Osteogenesis Imperfecta.** Seattle. Fri. Contact: Children's, (206) 526-2501.

April 14-16—**Children's ID Conference.** Seattle. Thurs-Sat. Contact: Children's, (206) 526-2501.

April 22-23—**Surgical Update 1994.** Tacoma. Fri-Sat. Contact: PCMS CME.

April 29—**Nuts, Bolts, and Innovation in Gastrointestinal Disease II.** Tacoma. Fri. Contact: PCMS CME.

May 6-7—**Cardiology Update.** Seattle. Fri-Sat. Contact: U/W.

May 8-11—**Fifth Annual Congenital Heart Disease in the Adult.** Stevenson. Sun-Wed. Contact: American College of Cardiology, (800) 257-4739.

May 20—**Clinical Guidelines.** Tacoma. Fri. Contact: PCMS CME.

June 5-8—**1994 Annual Meeting of the Society for Vascular Surgery and the North American Chapter, International Society for Cardiovascular Surgery.** Seattle. Sun-Wed. Contact: SVS/NA-ISCVS, (508) 526-8330.

June 17—**Interventional Radiology.** Seattle. Fri. Contact: U/W.

June 27-28—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS CME.

August 8-13—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Sat. Contact: U/W.

September 19-23—**Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 9-11—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

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CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibretes alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t1/2) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* [1 hour prior to PRAVACHOL (pravastatin sodium)], *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter2). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General**.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

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Articles

Antinuclear Antibodies and Breast Implants

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Based on a paper presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 1993.

Anecdotal reports have linked silicone breast implants to autoimmune diseases, with scleroderma being mentioned most often. In view of other environmental influences—such as silica mining and the toxic oil syndrome—thought to predispose to scleroderma, more systematic immunologic information on women with silicone implants is needed to assess any possible relation to autoimmunity.

A cross-sectional survey was carried out with 150 women, of whom 131 had implants. Group 0 consisted of 19 volunteer women without breast implants who felt healthy, group I was 38 volunteer women with breast implants who felt healthy, group II was 82 women with implants who had various symptoms, and group III was 11 women with implants who had autoimmune disease. Scleroderma was overrepresented in group III (6 of 11). Antinuclear antibodies were determined on Hep-2 cells, using serum dilutions of 1:16, 1:64, and 1:256. A positive test was indicated by 1+ or more fluorescence at 1:256. Antinuclear antibody tests were positive in 0% of group 0, 18% of group I ($P < .05$ versus group 0), 26% of group II, and 64% of group III. There was no correlation between antinuclear antibody positivity and type of implant, indication for implantation, time since first implantation, total number of implants, and report of implant leak or rupture.

Women with breast implants may be at risk for the development of antinuclear antibodies. Proof of such an association will require large-scale prospective studies and epidemiologic analyses.

(Claman HN, Robertson AD: Antinuclear antibodies and breast implants. West J Med 1994; 160:225-228)

Controversy has recently arisen as to whether women with breast implants may have autoimmune abnormalities. In particular, reports of patients with breast implants who also have scleroderma[1,2] or other autoimmune syndromes[3,4] have raised the possibility of "human adjuvant disease,"[5] which would be a counterpart of the inflammatory synovitis seen in rats after the administration of complete Freund's adjuvant. Because of the scarcity of systematic studies of a reasonably large number of women, the issue of whether breast implants are associated with autoimmune changes remains in doubt.[6] In fact, a definite association between breast implants and any autoimmune manifestation remains to be established.

Patients and Methods

We measured antinuclear antibodies (ANA) in the serum of four groups of women. The protocol was approved by the Internal Review Board of the University of Colorado (Denver) School of Medicine. Informed consent was obtained after the nature of the investigation was explained. In each group, women were studied consecutively without selection. Group 0 included 19 volunteer women who did not have breast implants and who considered themselves healthy. They entered the study and received payment for a blood specimen. Group I consisted of 38 women with breast implants who felt well and who volunteered to participate as control subjects. These women learned of our study by word of mouth and from the news media (there were no advertisements). They were pleased with their implants and thought that implants should remain available. Group II consisted of 82 women with breast implants who had various symptoms including fatigue, arthralgias, and myalgias, but in whom a definite diagnosis of autoimmune connective tissue disease could not be made. (Many of these patients have some of the characteristics of fibromyalgia,[7] but this was not included as a separate autoimmune condition). These women had been referred by plastic surgeons, rheumatologists, primary care physicians, through the news media, and through a local breast implant support group. Group III comprised 11 women with breast implants who had overt connective tissue diseases—6 with scleroderma, 2 with systemic lupus erythematosus (SLE), 2 with rheumatoid arthritis, and 1 with Sjögren's syndrome. These

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ABBREVIATIONS USED IN TEXT

ANA = antinuclear antibody
ANOVA = analysis of variance
SLE = systemic lupus erythematosus

women were referred by the same mechanisms as were the group II women. Their diagnoses were made by rheumatologists using criteria of the American College of Rheumatology.

Each woman in groups I, II, and III filled out a detailed questionnaire and had a history and physical examination. The questionnaire included historical data, such as the date of placement of all implants (some women had as many as 8), indications for implantation, type(s) of implant, reported overt leakage or rupture, the duration of symptoms, and other medical conditions. It also provided space for the women to describe the types and severity of their symptoms (if any).

Antinuclear antibody levels were measured in an independent laboratory. The technique used Hep-2 cell substrates in a standard indirect immunofluorescence assay, and the slides were read "blindly." Serum specimens were diluted 1:16, 1:64, and 1:256. An "ANA score" was established according to the degree of positivity at 1:256.

Statistical Methods

In the primary statistical analysis, we looked at ANA levels as a function of group. In various contexts, group was considered as a nominal variable (contingency table), an ordinal variable (nonparametric analysis of variance [ANOVA]), or an interval variable (parametric ANOVA and regression). In our analysis we also considered control variables such as the indication for implantation, the total number of implants, age at implantation, and type of implant.

Results

Table 1 gives the characteristics of the four groups of women. Significant differences in age were found across the four groups (ANOVA, $P < .01$). Group 0 was younger than the other three groups pooled (linear contrast, $P < .01$). Nevertheless, when age was considered as a covariable, there were no important differences in any of the analyses. There were no significant differences among groups I, II, and III with regard to the indications for or types of implants (contingency table, ANOVA). Most of the implants (95%) contained silicone gel, and 66% were inserted for cosmetic reasons. Nearly all (99%) of the women were white.

Figure 1 shows the results of the ANA tests. A positive ANA test over all groups was not correlated with age (unpaired *t* test). This increase in ANA positivity from group 0 to group III is significant (contingency table, 3 degrees of freedom; $P < .01$; logistic regression, $P < .01$), but it is independent of age. The prevalence of ANAs in women with implants who felt well (group I) was significantly greater than in healthy controls without implants (group 0) (unpaired *t* test, $P < .05$). If group III is omitted from the analysis because of possible ascertainment bias—that is, they entered the study knowing that they had autoimmune disease—the prevalence of ANAs was still strongly related to groups 0 to II (contingency table, $P < .05$; logistic regression, $P < .05$).

For groups 0, I, and II, the patterns of positive ANA staining were almost exclusively of the fine speckled type, and the "ANA profiles," that is, anti-double-stranded DNA, anticentromere, anti-SS-A, anti-SS-B, and antiribonucleoprotein assays, were negative.

As shown in Table 2, for women with positive ANA tests, mean ANA scores were similar for groups I and II

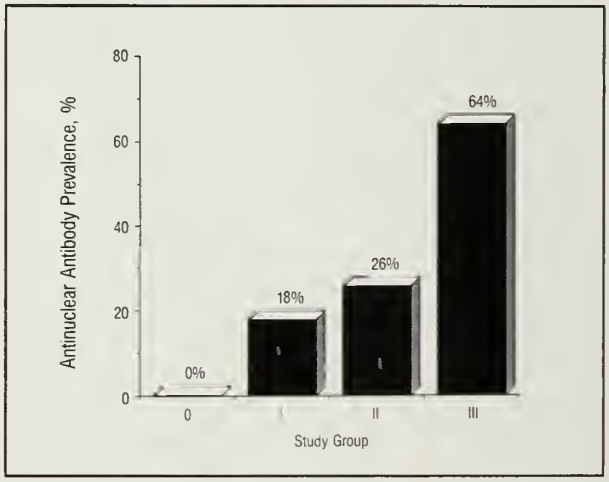

Figure 1.—The graph shows the prevalence of antinuclear antibodies at a titer of 1+ at 1:256 or stronger in four groups of women. See Table 1 for a clinical description of the four groups.

TABLE 1.—*Characteristics of 150 Women With Breast Implants*

Group	Clinical Characteristic	Subjects, No.	Age, yr ± SD	Implant Type*†			Implant Indication*		
								Reconstruction	
				Silicone	Saline	Double Lumen	Cosmetic Augmentation	Fibrocystic Disease	Cancer
0	No implants, healthy	19	38.8 ± 8.5						
I	Implants—well	38	45.2 ± 9.0	29	3	4	29	2	7
II	Implants—fatigue, musculoskeletal symptoms	82	47.2 ± 8.9	63	4	14	49	19	14
III	Implants—autoimmune disease	11	49.9 ± 10.7	10	0	1	8	2	1

*Information regarding implant type and the indication for implantation is not provided for group 0, as this is the control group.
†The type of implant is unknown for 2 women in group I and 1 woman in group II.

TABLE 2.—*Antinuclear Antibody (ANA) Scores by Group*

Group	Women, No.	Women With Positive ANA Test	Mean ANA Score* of Those With Positive ANA Test
0	19	0	NA
I	38	7	1.6
II	82	21	1.8
III	11	7	2.9

*The ANA score is determined by the degree of positivity at a dilution of 1:256:0 positivity = ANA score of 0, 1+ positivity = ANA score of 1, 2+ = 2, 3+ = 3, and 4+ = 4.

but significantly higher for group III when compared with groups I and II combined (unpaired t test, $P = .01$).

In group III, the ANA details were as follows: Of the six patients with scleroderma, three had the CREST syndrome (calcinosis cutis, Raynaud's phenomena, esophageal dysfunction, sclerodactyly, and telangiectasia; two were positive for ANA and anticentromere, and one was negative for ANA). Three women had diffuse scleroderma. Two had positive ANA tests (one with speckled and one with nucleolar patterns), and one did not (ANA-negative). Both patients with SLE had speckled ANAs. One had anticentromere antibodies, and the other had SS-A and SS-B antibodies. The patient with Sjögren's syndrome had ANAs, speckled pattern, and SS-A and SS-B antibodies. One patient with rheumatoid arthritis had ANAs, speckled pattern; the other patient with rheumatoid arthritis was ANA-negative. The one patient with diffuse scleroderma who was tested for Scl 70 was ANA-negative.

Possible implant rupture was assessed on the basis of history and findings at physical examination, mammography, or surgery; these data were correlated with ANA positivity. In group I, there were three ruptures (33% ANA-positive); in group II, there were 23 ruptures (22% ANA-positive). In group III, five women had ruptured implants, and all of the women were ANA-positive. Five women had no ruptures, and two were ANA-positive (40%). In one woman who was ANA-negative, the possibility of rupture could not be adequately assessed.

The period of time from first implantation to date of clinic visit (± standard deviation) was 10.0 ± 5.9 years (group I), 11.9 ± 6.1 years (group II), and 15.3 ± 4.3 years (group III). Although these do not differ significantly from each other taken in pairs, when group status (I to III) is considered as a continuum, group is correlated positively with time since first implantation ($P < .01$). Thus, women with connective tissue disease (when seen) had implants far longer than women with fatigue and musculoskeletal symptoms (group II) or women without symptoms (group I). The length of time from first implant to symptoms did not differ from group II (5.5 years) to group III (6.0 years).

There was no association between ANA positivity and type of implant, indication for implantation, or time since first implant.

When a multiple logistic regression analysis was carried out using group, age, number and duration of implants, possible leak, indication for implants, and type of implant, only group status remained significantly correlated with ANA positivity.

Discussion

In these studies we examined the relationship between breast implants and autoimmunity by measuring antinuclear antibodies in a cross-sectional analysis.

The following are the main findings:

- Significant positive ANA tests occur with a higher-than-expected frequency (18%) in women with breast implants who consider themselves healthy, when compared with controls (0% positive ANA tests);
- Many women with breast implants have a variety of complaints, including fatigue and musculoskeletal symptoms, that postdate the implants; they also have positive ANA tests (26%);
- In women with breast implants in whom connective tissue disease later developed, scleroderma was far more prevalent than rheumatoid arthritis or SLE.

We are cognizant of various types of bias that may exist in patient accrual. As both groups 0 and I felt well and had never had previous ANA testing, there was no ascertainment bias in these groups with regard to ANA positivity. The prevalence of antinuclear antibodies in healthy women without implants (group 0) was 0 in 19 (0%). The prevalence of positive ANA tests in healthy women depends on the criteria used for "positive." A recent study indicated that 5% of apparently healthy women had an ANA titer of 1:40.[8] If we used 1:64 as a criterion of positivity, 1 of 19 women in group 0 had a positive test, but at 1:256, none of the women had a positive ANA test. Thus, our results in group 0 are comparable to those of other investigators. An 18% prevalence of antinuclear antibodies in group I, a comparable group of well women with breast implants ($P < .05$ versus group 0), was unexpected. Whether autoimmune disease will develop in these women is not known. One study has shown that 12% of asymptomatic women testing positive for one or more specific antinuclear antigens, including anti-DNA, anti-SS-A, and anti-SS-B, observed for five years had signs or symptoms suggestive of autoimmunity.[9] Thus, it is possible that asymptomatic women in group I who had ANAs will in the future move into group II.

Women in group II have various symptoms including severe fatigue, musculoskeletal aches and pains, and stiffness. In no case did they meet the criteria for recognizable autoimmune syndromes. A few studies have been done of women similar to those in group II but who are not recorded as having implants. Patients with fibromyalgia (86% women) had a 9% prevalence of a positive ANA test at a titer of 1:64.[10]

Group III women with overt autoimmune disease had the highest prevalence and titer of ANA, consistent with their diagnoses. The relative preponderance of scleroderma in group III (6 of 11 patients) is in accord with the general anecdotal literature where breast implants have been associated more with scleroderma than with SLE or

rheumatoid arthritis. Although the precise prevalence of scleroderma is not known,[11] it is generally agreed to be far less common than rheumatoid arthritis. Thus, the existence in group III of six patients with scleroderma but only two with rheumatoid arthritis might be considered strong evidence pointing to an association between breast implants and scleroderma. Nevertheless, the anecdotal reports that emphasize scleroderma may also make it more likely that women with breast implants and possible or actual scleroderma will seek to enter research protocols. This point remains unresolved.

The procedure of breast implantation itself is unlikely to explain the difference in ANA prevalence between groups 0 and 1. There have been no reports associating ANA positivity with surgical procedures. With regard to the tissue damage involved, women in all groups had children, and the tissue damage associated with parturition is probably greater than that associated with implant placement.

While this study was being prepared for submission, Press and co-workers reported the findings of a similar series of women.[12] Of 24 patients with implants, 11 had diagnosed connective tissue disease, 7 with scleroderma and 10 with positive ANA tests. The other 13 women had rheumatologic symptoms, including myalgia, fibromyalgia, and chronic fatigue syndrome. Of these 13, 7 (54%) had positive ANA tests. The specificity of the antinuclear antibodies did not differ from that seen in similar patients without implants. The results of our studies are thus similar to those of Press and associates.

Another recent article described the cases of women with silicone implants.[13] There are similarities and differences between this report by Bridges and associates and our study. The prevalence of ANA positivity (1:80) was 8% in 12 patients with implants without clinical symptoms, whereas in our group 1, 18% had ANA positivity at 1:256. The prevalence of ANA positivity in all 156 patients with implants who were symptomatic was 22%, but it is unclear how much ascertainment bias existed in the accrual of these women. Antinuclear antibodies were found in 13 of a subgroup of 29 women with connective tissue disease (a prevalence of 45%), comparable to our group III. It is of interest that 14 of these 29 women had scleroderma-like illnesses.

These results suggest that women with breast implants may be at risk for autoimmunity. This cross-sectional study should be regarded as a hypothesis-generating probe. Larger and more carefully executed analytic studies are needed to test the hypothesis that a relationship exists between breast implants and autoimmunity.

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Articles

Is Needle-Directed Breast Biopsy Overused?

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We undertook this study of needle-localized breast biopsy—a frequently done surgical procedure—to examine current practice patterns and to determine if the technique is overused in any group of patients. From a retrospective review of medical records of all patients who had needle-localized breast biopsy at a teaching hospital between June 1, 1988, and October 31, 1990, we found that a total of 125 were done: 24 biopsy specimens showed malignancy (19%). Mammographic indications for biopsy were microcalcification (n = 62, or 50%), mass or density (n = 60, or 48%) and mass and calcifications (n = 3, or 2%). Indications for biopsy in patients with cancer were microcalcification (14 patients) and mass or density (10 patients). The incidence of malignancy increased with age. In patients younger than 40 years, no biopsy showed malignancy. Only 2 of 30 biopsies done in patients younger than 50 showed cancer (7%). Breast cancer was most frequently discovered in patients in the seventh and eighth decades of life, and this group accounted for 75% of "positive" biopsies. Needle-localized breast biopsy is a useful technique in the early diagnosis of breast cancer. Although indications for the procedure should remain liberal, in women younger than 50, the percentage of biopsies that reveal malignancy is low.

(Shields MW, Smith RS, Bardwil MF, Harness JK: Is needle-directed breast biopsy overused? West J Med 1994; 160:229-231)

Mammographically directed biopsies of occult breast lesions are rightly heralded as a useful method to lower the breast cancer death rate in women.[1,2] Indeed, this has been shown to be the case for women older than 50. Although about 5% of all mammograms are suggestive of malignancy, leading to biopsy,[3] the "positive" biopsy rate is only 20% to 25%,[4,5] and several studies have shown a positive biopsy rate as low as 3.5%.[4]* About 2,000 women must be screened mammographically before a single one benefits.[3] We undertook this study to evaluate our use of mammographically directed biopsies and to determine if the process is overused in any group of patients.

Patients and Methods

We retrospectively reviewed 125 consecutive mammographically directed biopsies done between June 1, 1988, and October 31, 1990. All patients who had mammographically directed biopsies during this period were included in this review, regardless of the specific indications for biopsy or previous risk factors. The patients ranged in age from 31 to 83 years with a mean age of 57. The lesions from which biopsies were taken were nonpalpable mammographically detected lesions. The patients were admitted through the same-day surgery center, taken from there to the mammography department where localization needles were placed into the lesions, then to an operating room where the biopsies were done under local anesthesia with intravenously administered sedation. The specimens were sent for mammography to confirm that the lesions in question were indeed removed, then to the pathology department for histologic evaluation. All patients were affiliated with the military and treated at Oakland (California) Naval Hospital: 99 were wives of retired military personnel, 17 were wives of active-duty personnel, 2 were active-duty service women, 1 was a retired service woman, and the rest were other types of military dependents (such as dependent mothers) or unspecified military personnel. Most patients (103 of 125) had no history of breast disease. Of the 125, however, 22 patients had a history of either contralateral breast cancer, a biopsy of a benign lesion, or other indication of previous breast disease: 9 patients had previous contralateral breast cancer, 7 had a biopsy based on an interval mammographic change, 5 had had one or more previous biopsies of benign lesions, and 1 patient had a one-year history of a yellowish brown nipple discharge.

Results

Of 125 total biopsy procedures, 24 (19%) revealed cancer ("positive biopsy"; Table 1). The average and median ages of the patients with positive results were 63 and

*See also the editorial by F. M. Hall, MD, "Needle Biopsy of Probably Benign Nonpalpable Breast Lesions," on pages 276-277.

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TABLE 1.—*Relation of Age to Positive Biopsies*

Age, yr	Biopsies, No.	Positive Biopsies No.	Positive Biopsies %
30-39	7	0	(0)
40-49	23	2	(9)
50-59	27	4	(15)
60-69	50	13	(26)
≥70	18	5	(28)
All ages	125	24	(19)

65 years, respectively. The average age of those whose biopsy results were benign ("negative biopsy") was 58 years. Of the 24 cancers, 19 were invasive and 5 were in situ. Of 19 patients with invasive cancers, 10 had an in situ component. Of the nine patients with previous contralateral breast cancer, three had breast cancer diagnosed in the new specimen. Of seven patients who had biopsies because of interval mammographic changes, two proved to have positive current biopsies. One of five patients who had had previous negative biopsies had newly diagnosed breast cancer. The only patient with a pigmented (brownish yellow) breast secretion had carcinoma.

The most common findings in the 101 patients with benign breast lesions were related to fibrocystic changes: epithelial hyperplasia (62 patients), cystic changes or formation (55 patients), apocrine metaphasia (55), sclerosing adenosis (34), periductal mastitis (duct ectasia; 27), fibroadenoma (25), fibrotic or sclerotic lesions (16), and papilloma or papillomatosis (14).

Other benign histologic findings occurring in four or fewer specimens were atypical ductal hyperplasia, atypical lobular hyperplasia, fat necrosis, arterial wall calcification, lymph nodes, ductal adenoma, hamartoma, suture granuloma, and chronic inflammation.

The fact that epithelial hyperplasia is a marker for an increased risk of breast cancer indicates that about 60% of the benign lesions warranted strict follow-up. The percentage of biopsies revealing malignancy increased with advancing age (Table 1).

When the 30 patients younger than 50 were examined as a subgroup, only 2 (7%) had positive biopsies. The 95 patients older than 49 had a positive biopsy rate of 23% (n = 22). Our data are similar to the 12% and 26% positive biopsy rates in patients younger than 50 and older than 49 in a study of 1,261 mammographically directed biopsies.[5]

Table 2 shows that the positive biopsy rate for biopsy indications of mammographic microcalcifications and masses is about equivalent at 22% and 17%, respectively.

Discussion

Our study confirms the clinical usefulness of mammographically directed biopsies in detecting nonpalpable breast cancers with a positive predictive value of 19% (24 of 125). This compares favorably with the national average of about 20%. The results of four of five biopsies were still benign, however, thus exposing women to small but definite risks of complications such as hematoma, infection, and cosmetic deformity and the anxiety of undergoing a diagnostic procedure to rule out cancer. A positive predictive value of 28% can be obtained by strictly scrutinizing mammograms for evidence of malignancy.[3] The following criteria have been recommended as acceptable mammographic findings for doing a biopsy[3]: clustered calcifications, suggestive distortion of local architecture, a typical spiculated image, abnormal ducts or unresolved cysts, and interval mammographic change. In a retrospective review of 400 mammographically directed biopsies, Hall and co-workers found that the positive predictive value could be increased to 39%.[6] This approach to abnormal mammograms would have resulted in doing biopsies in four patients with noninvasive and one with invasive cancer. Guided needle aspiration of possible cysts is another means of reducing the number of negative biopsies.[7]

There is a false-negative rate with the initial mammographic screen; the sensitivity of mammographic screening is about 96%,[3] thereby missing 4% of malignant tumors. Despite the occurrence of some false-negative mammograms, mammographic screening has been shown to reduce the death rate from breast cancer in women older than 50 years.[1,2]

Data suggest (Table 2) that microcalcifications merit slightly more respect as a possible indication of malignancy; other studies have found that mammographic masses are the more important finding.[5,8] Of interest is that in one study 75% of intraductal carcinomas were associated with clustered calcifications.[8] Data from our study support these findings. Of 24 biopsies revealing cancer, intraductal carcinoma was an important component in 15 cases. Of these 15 cases, 11 (73%) were detected mammographically as abnormal microcalcifications. This correlates with the histologic finding of calcification occurring in the necrotic center of packed masses of malignant intraductal cells. Another relevant finding is that at least 60% of the lesions classified as benign contained epithelial hyperplasia, which in itself is a marker of increased risk for malignancy. This suggests that mammography identifies not only a subset of women with malignancy in nearly 20% of biopsies, but also a subset with an increased risk of future malignancy in 60% of biopsies showing benign lesions.

Our data and those of others suggest that patients younger than 50 have about a 90% chance of a negative biopsy. Whereas the benefits of mammographically directed biopsies are well established, we suggest that pa-

TABLE 2.—*Relationship of Mammographic Finding to Biopsy Result*

Indicotions for Biopsy	Potients, No.	Positive Biopsies No.	Positive Biopsies %
Microcalcifications	62	14	(22)
Mass	60	10	(17)
Mass and microcalcifications	3	0	(0)

tients younger than 50 with questionable findings on a mammogram may be better served by the following:

- Observation for a brief period, followed by mammographic follow-up; and
- A review of the abnormal mammogram by a radiologist with particular skill in this area.

Of course, there is no substitute for sound clinical judgment; a 31-year-old patient in our study with a history of right-sided breast cancer had a justifiable negative biopsy of the left breast due to an abnormal mammogram. Breast cancer certainly does occur in younger age groups, but this should not prevent the judicious observation of younger patients with questionable mammographic indications for biopsy.

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IN THE SUMMER OF 1993, HE DISCOVERS IN HIS MEDICINE CHEST A COMPLIMENTARY BOXED BAR OF SOAP HE ACQUIRED IN THE PALACE HOTEL, BELGRADE, DURING HIS 1988 TENURE IN YUGOSLAVIA AS A FULBRIGHT FELLOW

Oh, I am returning this to you,
thank you, for your coming clean,
not for your cleansing, no, not that,
but for the washing from your hands
of those stubborn stains I have been

reading about with disbelief, my memories
of Sarajevo including no one sufficiently
astonished then—certainly not me—
at the peacefulness of your most
rainbowed and open city, like

a feast spread out for all comers
at the foot of the hills. So I return
this soap to you intact—the bar, that is,
not you, who are barely intact. Its suds will rise
and take you by the hand, provided you first

remove all your clothing and stand
in the River Drina or Sava or Danube,
as if for a baptism, before letting yourself
fall trustingly backwards into the arms
of the water like an actor warming up

with his partner for a performance of
Waiting for Godot by the Mostar Players.
Meanwhile, without this bar, I will of course
be getting dirty here rehearsing
my own history in my own place.

PHILIP DACEY©
Lynd, Minnesota

Articles

Patients' Understanding and Use of Advance Directives

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The Patient Self-Determination Act was implemented in December 1991. Before and after its implementation, we used a structured interview of 302 randomly selected patients to determine their awareness, understanding, and use of advance directives. Implementation of the Act did not have a major effect on these. Although more than 90% of patients were aware of the living will, only about a third selected the correct definition or the correct circumstances in which it applied, and less than 20% of patients had completed one. About a third of patients were aware of a Durable Power of Attorney for Health Care and chose the correct definition, and about half identified the correct circumstances in which it applies; less than 10% had completed such a document. Surprisingly, patients who said they had completed advance directives did not demonstrate better understanding of these documents.

Our results indicate that many patients, including some who have completed advance directives, do not fully understand them. It may be unwise to regard these documents as carefully considered, compelling statements of patients' preferences. Appropriate responses to our findings include increased public education, revising state statutes to bring them into congruence with public perception, and expanding the dialogue between physicians and patients.

(Jacobson JA, White BE, Battin MP, Francis LP, Green DJ, Kasworm ES: Patients' understanding and use of advance directives. West J Med 1994; 160:232-236)

The Patient Self-Determination Act of 1990 is a public policy intended to inform patients about some of the steps they can take to exercise control over their medical care if they become incompetent or unable to express their wishes.[1] The Act, implemented December 1991, requires that health care institutions inform all adult patients about the relevant state laws and hospital policies that apply to advance directives. Advance directives such as the Living Will and Durable Power of Attorney for Health Care putatively enable patients who wish to exercise control over their future health care to do so. The Patient Self-Determination Act also requires that hospitals inquire whether the patients have completed advance directives.

The Utah Personal Choice and Living Will statute specified, as do the statutes of 44 states, that a living will applies only when the person who completed it is incompetent and terminally ill. The Utah statute required that artificial nutrition and hydration be administered to patients who have a living will, unless they specifically noted that they refused this treatment. The statute allows a person to appoint someone to make medical decisions for him or her if the granter of this durable or special power of attorney for health care becomes incompetent.[2]

In the relatively short period of time since advance directives have been available, several studies have investigated patients' attitudes about them.[3,4] Patients appear to be receptive to questions about their preferences for medical care, and they seem attracted to the concept of a document that would ensure that their preferences would be honored. On the other hand, few patients—less than 15% in most studies—have actually completed a living will.[4,5] Few studies have investigated how many patients have designated a durable power of attorney for health care, but the highest estimates do not exceed 15%.[5]

No studies have deeply probed patients' knowledge about advance directives. We used extended structured interviews that included clinical vignettes to investigate how well patients admitted to a hospital understood advance directives. We examined the effect of the implementation of the Patient Self-Determination Act on patients' understanding and use of advance directives. We found that patients' understanding of these documents, especially the living will, was poor and not improved by the implementation of the Act. We propose several steps that could ensure a better match between end-of-life care and patients' preferences.

Patients and Methods

At the LDS Hospital, Salt Lake City, Utah, the Patient

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Self-Determination Act was implemented by providing all patients a one-page summary of state statutes and hospital policies regarding advance directives. Patients' primary care nurses ask patients if they have completed an advance directive.

For this study we planned to complete interviews with at least 200 persons before the Patient Self-Determination Act was implemented and 100 afterwards. We conducted bedside interviews with randomly selected patients admitted to LDS Hospital, a 500-bed acute-care hospital. The interviews were obtained from August 12 to November 22, 1991, before implementation of the Act, and from February 24 to May 15, 1992, after the Act was implemented. The interviews were conducted by trained personnel of the Division of Medical Ethics.

The questionnaire was designed to assess patients' awareness and understanding of a living will and of a durable power of attorney for health care. We asked patients to choose the definition for each document from a list of seven choices (Figure 1), to identify the clinical circumstances in which each document applies, such as incompetence, terminal illness, or both, and to determine the effect of each document in a series of clinical vignettes. We also inquired whether the patient had completed either or both of these documents. The interview required about half an hour to conduct. The questionnaire was pretested and revised to ensure the greatest possible clarity.

To be eligible for this study, patients had to be admitted within the previous 48 hours and to be 18 years of age or older. Starting at the top of a computer-generated random list of eligible patients, interviewers investigated if the patient was available to be interviewed and if the patient, as judged by his or her nurse, was mentally and medically able to participate in the study. Patients were eligible to be interviewed regardless of the acuity of their illness or unit to which they were assigned. Patients who did not speak English were not interviewed. Available patients deemed capable were approached and asked if they would consent to be interviewed. Midway through the interview, patients were asked if they wished to continue.

Factors associated with answers to questions and the completion of advance directives were statistically analyzed using χ^2 and Fisher's exact test.

What do you understand a Living Will is? [Same question and choices for Durable Power of Attorney for Health Care]

- A document that says how your money and property will be distributed after you die
- A document that says how your body should be handled if you die
- A document that specifies what life-sustaining treatment you don't want if you have a terminal illness and are unable to communicate
- A document that authorizes someone else to act for you in financial and other personal matters
- A document that specifies who should make medical decisions for you if you are unable to do so
- A document that says you are willing to donate your organs if you die
- A document that specifies a way you can give money to someone or an institution and receive a tax benefit
- Don't know
- Other

Figure 1.—Shown enclosed in the box is the question patients were asked to indicate their understanding of a living will or a durable power of attorney for health care.

TABLE 1.—*Percentage of Patients Who Are Aware of and Who Understand Advance Directives Before and After Implementation of the Patient Self-Determination Act (PSDA) (n=302)*

	Advance Directives			
	Living Will		Durable Power of Attorney	
Awareness and Understanding	*Before PSDA (n=202), %*	*After PSDA (n=100), %*	*Before PSDA (n=202), %*	*After PSDA (n=100), %*
Awareness	91	94	32	39
Chose single correct definition	31	41	29	37
Chose correct circumstance(s)	28	32	46	54

Results

Before our hospital implemented the Patient Self-Determination Act, we completed interviews with 202 of 361 (56%) patients that we approached. Afterwards, 100 of 195 patients (51%, P = not significant [NS]) completed the interview.

Our study population, 41% male, with a mean age of 48 years, did not differ significantly from the inpatient population during the interview periods. Like the patients at our hospital generally, our subjects were predominantly white, and 48% said they belonged to the Latter Day Saints religion. Most of our interviewed patients (91%) had graduated from high school; 68% had some additional education, and 29% had completed four or more years of higher education. Patients in the two parts of our study did not differ significantly with respect to the above factors.

Table 1 shows awareness and two levels of understanding of living wills and durable powers of attorney for health care by our study subjects. There were no significant differences after the Patient Self-Determination Act was implemented. When asked to define only a living will or a durable power of attorney, 10% and 2%, respectively, of patients chose to define both documents. Only 6% of patients in both periods selected the correct definition and identified the clinical requirements for both types of advance directives. The 30 patients who correctly answered these questions about the living will were not significantly different from patients who answered incorrectly with respect to sex, age, religion, or race. They were more likely, however, to have finished high school (100% versus 89%, $P < .05$). The 41 people who answered these questions accurately about the durable power of attorney

TABLE 2.—*Percentage of Patients Who Correctly Indicated the Effect of an Advance Directive in a Paradigmatic Case, or a Case That Involved a Persistent Vegetative State (PVS)*

	Potients Understood Effect of Advance Directives, %			
Potient Self-Determinotion Act Implemented	Living Will in Porodigm Cose	Living Will in PVS	Duroble Power of Attorney in Porodigm Case	Duroble Power of Attorney in PVS
Before Act (n = 202).....	50	24	75	71
After Act (n = 100).....	58	16	76	78
Significance, *P*.....	NS	NS	NS	NS

NS = not significant

differed from those who answered incorrectly by age (76% versus 47% were younger than 51, $P < .001$), and they were also more likely to have finished high school (100% versus 88%, $P < .05$), but they did not differ significantly by sex, religion, or race.

Most patients who had heard of advance directives reported that the media was the source. Less than 10% said they heard about them from a physician or nurse. During the second study period when written information about advance directives was given to patients by the hospital, 24% and 16%, respectively, recalled receiving that information about the living will and durable power of attorney.

We also assessed patients' understanding of advance directives with clinical vignettes. In one vignette, a paradigmatic case, "The patient has cancer, cannot communicate his or her wishes, and is expected to die within one month. The patient has respiratory failure and will die sooner unless a ventilator is used."

In a second vignette, "The patient has been in an accident and is now in an irreversible coma (persistent vegetative state). Nutrition and hydration (food and water), delivered intravenously or by a tube inserted into the stomach, are necessary for survival."

Table 2 shows the proportion of patients who correctly indicated the effect of each advance directive in these cases. Notably, about 80% of patients made an incorrect choice about the effect of a Utah living will in the case of the patient in a persistent vegetative state: 44% indicated that the living will would prevent the provision of nutrition and hydration, 11% thought the living will would require these measures, and 22% said they did not know the effect of the living will in this case. Only 21% chose the correct answer, namely, that the living will did not apply in this case because the patient was not terminally ill.

Before the Patient Self-Determination Act was implemented, 15% of our subjects reported completing a living will and 5% a durable power of attorney for health care. Afterwards the proportions were 18% and 7%, not a significant change. Of the 48 patients who said they had a living will, 16 said they also had a durable power of attorney. Two other patients reported that they had only a durable power of attorney.

Although Table 2 includes the answers of all the respondents to our survey, we separately examined the responses of patients who reported that they had completed either a living will, a durable power of attorney, or both. When we examined the demographics of these patients and those in our survey who had not completed such documents, we found that patients with living wills were significantly more likely to be older than 51 years than those without them ($P < .001$). These patients were also significantly more likely to have graduated from high school (98% versus 89%, $P = .04$) and to have completed additional years of education ($P = .03$). We noted no significant differences between those patients who reported completing a durable power of attorney and those who did not, although those with the document were more likely to be older than 51 years.

Surprisingly, patients who said they had completed a living will did not understand this document's definition or clinical application better than patients who said they had not completed one. Of the 48 patients who reported having such a document, 16 (33%) identified the single correct definition, and 19 (40%) correctly identified the circumstances in which the Utah Living Will applied. Presented with the paradigmatic vignette, living will holders did not perform better than those without the document (P = NS). Of the 48 patients, 35 (73%) correctly said that it would prevent the use of a ventilator.

When presented with the vignette about a patient in a persistent vegetative state, in which the Utah Living Will would not apply, living will holders again did no better than those without the document (P = NS): 31 (65%) said the living will would prevent health care professionals from providing nutrition and hydration, 9 (19%) correctly said the living will does not apply, 6 (12%) said they did not know, and 2 (4%) said the living will would require artificial nutrition and hydration.

Like the patients who had completed a living will, most patients who had completed a durable power of attorney for health care did not have a significantly better understanding of the definition of the document or the circumstances in which it applies than the rest of the surveyed population. Of the 18 patients who said that they had appointed a proxy for health care decisions, 4 (22%) chose the single correct definition, and 9 (50%) correctly identified the circumstances in which a durable power of attorney applies. When presented with the paradigmatic vignette, 15 (83%) indicated correctly that the proxy had the legal right to decide about the use of a ventilator.

We asked patients whether a living will or durable power of attorney, as the final expression of their wishes, should be the determinant of their care. We asked them under what circumstances the preferences expressed in a living will or by an appointed proxy should be overridden. Their responses are shown in Table 3. These responses did not change significantly between study periods. Remarkably, a similar proportion of patients who said they had executed an advance directive, which is legally binding, said that it should be overridden.

Discussion

Before drawing conclusions from our study, certain limitations must be acknowledged. Interpreted as a response rate, the 55% of patients who completed the interview would appear to be a rate that could provide results

TABLE 3.—*Patients' Opinions About Overriding Advance Directives*

	Should Directive Be Overridden?								
	All Respondents (n=302), %			Patients With Living Wills (n=48), %			Potients With Duroble Powers of Attorney (n=18), %		
Advonce Directive	Yes	No	Not Sure	Yes	No	Not Sure	Yes	No	Not Sure
Living Will									
Physicians should ignore living will instructions if they think to do so is best for the patient	20	63	17	17	71	12			
Physicians should ignore living will instructions if family members ask them to	19	66	15	23	73	4			
Durable Power of Attorney									
Physicians should ignore proxy's instructions if they think to do so is best for the patient	21	53	26				0	78	22
Physicians should ignore proxy's instructions if family members ask them to	20	55	25				17	72	11

representative of a population if there were no systematic and confounding reasons for refusing to participate. We asked patients why they refused and were given a variety of reasons including discomfort, the presence of visitors, anxiety, fatigue, and a lack of interest in participating in such a survey. It is unlikely that patients refused to be interviewed because of their extensive knowledge about advance directives. Thus, it seems that our interviewed sample was not likely to underestimate the level of knowledge in our hospital population. Certainly a survey in a single hospital, particularly with a population that is primarily white and well educated, cannot be assumed to be representative of the knowledge and opinions of other segments of the American population. Each of these possible biases in our sample would seem to suggest, however, that our results would overestimate rather than underestimate the level of understanding of advance directives in the rest of the population. Although we interviewed patients in only one hospital, our patient group was more inclusive with respect to age than those in other studies of patients' knowledge about advance directives.[4] Although a higher proportion of our patients were members of the Latter Day Saints religion than might be found elsewhere, we did not find religion to be a significant factor with respect to awareness, understanding, and use of advance directives. The correctness of our patients' answers was judged with respect to the Utah Personal Choice and Living Will statute as of 1992. Patients in other states may be more or less knowledgeable about their state's laws, or the statutes may be more aligned with public perception (or both).

Our study differs from others in that we assessed the knowledge of adult patients of all ages, but who had a common characteristic, namely a need to be in the hospital. Thus, although our sample is obviously different from a random sample of the United States public, a healthy population, nursing home residents, or a group selected based on being older than 65, patients in our study certainly had a reason to be concerned about and affected by decisions regarding their health care. In a survey of patients admitted to a tertiary care hospital such as ours where many admissions are anticipated and elective, we might expect to have encountered a higher proportion of patients who had completed advance directives than was found to be the case. We did find, as did other investigators, that patients are generally aware of advance directives,[4,5] but the level of patient knowledge and understanding remains poor.

There are several other possible limitations to consider because the number of persons in our survey who had actually completed a living will and, particularly, a durable power of attorney was relatively small. Therefore, it may be premature to conclude that patients who have completed these documents do not differ significantly in their knowledge about them from patients who have not done so. Our interview subjects did not include patients who were unconscious, unable to communicate, or incompetent. These are the patients for whom advance directives might be useful. We have no information on the frequency with which these persons had previously executed advance directives or their knowledge about them. The competent patients we did talk with were obviously in an environment that could be stressful, and the accuracy of their answers may have been adversely affected by that. We also did not insist that patients who reported completing advance directives produce copies of them.

Despite these possible limitations, it appears that a significant proportion of the patients admitted to our hospital do not understand our state's advance directives very well. Implementing the Patient Self-Determination Act through a relatively passive program of distributing written information about advance directives has done little to improve patients' understanding. In our hospital, the Act has had little discernible effect on the low rate at which patients complete advance directives.

An unexpected result in our study was that even patients with advance directives frequently misunderstand them. Like patients without living wills, patients with them often failed to recognize the requirement for a terminal condition. Perhaps more surprising was that a sig-

nificant minority of patients who had executed advance directives thought they should be overridden if physicians or family members thought it best to do so.

Completing an advance directive did not seem to increase patients' knowledge about the document, but it may have had a benefit for these persons independent of the document's effect on medical decisions. The act of completing the directive may lower a patient's level of anxiety about death and the treatment associated with the end of life. That result has been suggested by the study of Henderson.[6] Our impression, as we interviewed these patients, was that they were proud and somewhat relieved that they had taken steps that they felt would control their care in circumstances in which they viewed a lack of control as frightening and burdensome. Completing a living will is unlikely to provide the kind of control they wanted in one of the circumstances they feared most.

When we recognized the discrepancy between patients' perceptions about the Utah living will and the statute, particularly with respect to the persistent vegetative state, we shared our findings with state legislators. They chose to amend the statute and include persistent vegetative state as an additional criterion that would make the living will operative.[7] This certainly will help some patients realize their expectations of end-of-life care. What remains unresolved, however, is the apparent paradox that a substantial minority of patients want their final expressions of personal preference to be overridden if their physician or family thinks it best to do so.

At this point then, despite the Patient Self-Determination Act, health care professionals are still likely to find that most patients who face end-of-life decisions have not completed advance directives. Even if patients have completed advance directives, clinicians should recognize that the directive(s) may be neither complete nor thoroughly understood expressions of patients' preferences. To encourage patients to complete advance directives without extensive education and counseling, or to strictly adhere to all advance directives without discussion, is unlikely to serve patient autonomy fully. Discussion with all patients before a crisis still seems the best way to ascertain patients' values, preferences, and goals for therapy.

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Conferences and Reviews

Magnetic Resonance Imaging and Measurement of Blood Flow

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Blood flow can be shown as a negative image with magnetic resonance spin-echo techniques or as a positive image with gradient-echo techniques. Phase contrast refers to techniques where structures can be seen because of flow-induced phase shifts. These techniques can show the presence (slow flow) and also the direction of flow. Gradient-echo techniques—including phase-contrast versions—can be used with cardiac synchronization to obtain multiple images during the cardiac cycle. These images can be viewed in a movie or cine format to provide dynamic information about blood flow. Blood flow can be measured by using contrast media in boluses or even more elegantly with phase-contrast methods. Clinical applications of flow measurements are growing rapidly. Phase-contrast or gradient-echo techniques can be used to create magnetic resonance angiography, which was first used to study the carotid bifurcation and intracranial circulation and is now being used throughout the body.

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With magnetic resonance (MR) imaging, flow has inherently high contrast relative to static tissues. Magnetic resonance angiography allows the cardiovascular system to be visualized and allows the structure and patency of vessels to be evaluated. Furthermore, current techniques can delineate the direction and quantity of blood flow as well as flow patterns throughout the cardiac cycle.

We review the current clinical use of imaging and the measurement of blood flow with MR imaging.*

Spin-Echo Imaging

In simple terms, MR imaging produces images from protons (or hydrogen nuclei) within the body. These nuclei behave like small spinning magnets. The nuclei are excited by radio-frequency pulses, and signal is received as the excited state decays. Magnetic gradients allow for a single tomographic slice of tissue to be excited selectively and for an image to be taken at a given time.[1]

Magnetic resonance imaging has usually used spin-echo pulse sequences whereby each slice of tissue receives a 90-degree excitation pulse followed by a 180-degree refocusing pulse before a signal is received. Blood protons within that portion of blood vessel that is in the slice of tissue receiving the 90-degree excitation pulse continue to flow out of the tissue slice during the refocusing pulse and readout; therefore, the vessel lumen is represented by a lack of signal (a signal void) in contrast to surrounding soft tissue. Turbulence of the spinning protons also contributes to the loss of signal associated with blood flow in spin-echo imaging. Thus, blood vessels can be reliably evaluated for patency on traditional parenchymal images when a signal void is found. Other factors, such as slow flow, can lead to increased signal in the presence of flow on spin-echo imaging. In summary, on spin-echo images an intraluminal signal void indicates blood flow and vessel patency, but the presence of signal in the vessel does not exclude the presence of flow.[2]

Gradient-Echo Imaging

Faster MR imaging methods, referred to as gradient-echo techniques, have proved to be more valuable for obtaining images of blood flow. With gradient-echo techniques, there is only a single (lower-flip-angle) excitation pulse, followed by the signal readout. Magnetic gradients perform the refocusing function before a signal readout, making the image of blood flow bright, rather than using the 180-degree refocusing pulse seen in traditional spin-echo imaging, where the image of blood flow is black. With the gradient-echo techniques, this sequence of events is performed rapidly and repeatedly to produce an image representing a single slice of tissue. During these repeated excitations, protons within the static tissue in the slice of interest quickly reach a state of partial saturation or exci-

*See also the editorial by C. B. Higgins, MD, "Ebb and Flow of the Circulation," on pages 275-276.

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tation. Within a vessel lumen, blood protons from outside the slice are constantly flowing into the slice of interest. These flowing protons are fresh, or not partially saturated, and therefore produce more signal intensity than static tissues during a signal readout. With gradient-echo techniques, this flow-related enhancement effect is unopposed by the previously described factors that usually lead to signal loss for traditional spin-echo imaging.

Although gradient-echo techniques are sensitive to blood flow, they are subject to error. Very slow flow remains a limitation, and thrombosed blood passes through a subacute stage when it is bright on gradient-echo images. The combination of spin-echo and gradient-echo images will provide adequate evaluation for the presence of blood flow and vessel patency in most patients.

Phase-Contrast Imaging

Phase-contrast techniques, which are relatively new magnetic resonance techniques, are the most sensitive to flow and are the most useful for distinguishing between slow and absent flow. Phase-contrast methods exploit the fact that protons (spinning magnets) that move through magnetic field gradients obtain a different phase (or alignment of individual spins relative to one another) from static spins. With conventional MR imaging methods, these phase changes are not utilized. By keeping track of these phase changes, images with controlled sensitivity to flow can be produced. Furthermore, an additional set of images is obtained in which flow is encoded so that in one direction it is black and in the opposite direction it is white. The intensity of black or white is directly related to velocity. Thus, these imaging sets not only confirm flow (even slow flow) but also display its direction and magnitude.[3-5]

Cine Imaging

Both gradient-echo and phase-contrast techniques can be employed along with cardiac synchronization to provide images representative of several phases of the cardiac cycle. These can then be viewed in a movie, or cine, format.

Cine gradient-echo methods are useful for obtaining images of dynamic processes, such as a beating heart. They provide some information about the presence of flow due to inflow enhancement. This flow information is only qualitative, however, because the signal intensity of flowing fluid has a complicated dependence on multiple factors.

Phase-contrast cine magnetic resonance, which depicts motion and flow throughout the cardiac cycle, can be used to evaluate the presence, direction, and temporal dynamics of flow both qualitatively and quantitatively. The ability to characterize direction, pulsatility, and complexity of flow not only improves diagnostic accuracy but may provide unique insights into pathologic processes. Phase-contrast cine MR imaging is particularly useful in areas not easily accessible by Doppler methods or where the complex flow of a disease process may provide confusing data. For example, in a patient with aortic dissection, the velocity-dependent contrast, with the intrinsic suppression of static structures, improves sensitivity to measuring slow flow and its differentiation from thrombus from the pelvic great vessels (Figure 1).[6-10]

Figure 1.—A dissection of the descending thoracic aorta is shown by an axial gated T1-weighted spin-echo image (**top**), an axial cine gradient-echo image (**middle**), and a corresponding phase-contrast image with flow encoded superiorly to inferiorly (**bottom**). Flow is seen in both lumens (on both sides of the intimal flap [**arrow**]). Note on the phase-contrast image that flow towards the head (ascending aorta) is black and flow towards the feet (descending aorta) is white.

Measuring Blood Flow

The ability to quantitate flow noninvasively is a poten-

Figure 2.—A collapsed image allows a vantage point on the circle of Willis. A phase-contrast magnetic resonance (MR) angiogram **(upper left)** is compared with a time-of-flight MR angiogram **(upper right)**. The latter is distinguished by the presence of orbital fat **(curved arrow)** and subcutaneous fat signal. The large white circle depicts the chosen volume of interest for rotational views, such as the frontal **(lower left)** phase-contrast projection depicted or the selected frontal projection from a basilar **(lower right)** circulation volume of interest. Also shown are the anterior cerebral arteries **(short thin arrows)**, middle cerebral arteries **(short broad arrows)**, posterior communicating arteries **(long broad arrows)**, basilar artery **(arrowhead)**, and the posterior cerebral arteries **(long thin arrows)**.

tially powerful aspect of MR imaging. Magnetic resonance imaging does not need an appropriate acoustic window as required by ultrasonography. It provides excellent temporal data throughout the cardiac cycle with cine techniques, and it easily evaluates the edges of vessels.

Techniques used to measure blood flow take advantage of either time-of-flight effects or phase-shift effects. Time-of-flight effects refer to the bulk motion of protons, or spins, relative to the timing of a pulse sequence. Quantitative techniques based on time-of-flight effects are referred to as bolus tracking. In simple terms, a plug of blood within a blood vessel is tracked (by selective excitation or saturation) a measurable distance in a known amount of time. The average velocity of flow can then be calculated. Flow can then be calculated by multiplying the cross-sectional area of blood flow by the average velocity of flow through that area. The accuracy of these bolus tracking techniques can be limited by poor edge definition of the tagged (or saturated) plug of blood and by errors in measuring a cross-sectional area. With slow flow, small displacements of tagged blood are more difficult to measure accurately. Nevertheless, studies have shown close agreement between Doppler and bolus tracking measurements of peak flow velocity and velocity-integral measurements in the aorta.[11]

As described for phase-contrast imaging, the motion of protons in the presence of a magnetic field gradient produces a change in phase that is actually proportional to the velocity of the motion. By dividing up a bolus of blood into many small volumes and using phase changes to calculate the average velocity for each small volume, accurate peak and average flow velocities can be calculated. Flow can then be calculated after measuring the cross-sectional area of the blood vessel. Cine phase-contrast techniques allow pulsatile flow to be measured and flow patterns throughout the cardiac cycle to be delineated. Quantitative measurements based on phase shifts have been validated both in vitro and in vivo using implanted flow probes.[12,13]

Clinical Application

The highly accurate and noninvasive MR techniques for measuring blood flow are now widely available, but they have just begun to be used clinically. These tools have been used largely for research in a number of areas. Flow rate waveforms and average flow rates have been measured in the cerebral circulation of normal persons[14] and in patients with arteriovenous malformations.[15] Measuring flow within the aorta directly has been suggested as a method for evaluating cardiac output, aortic compliance, and coronary artery blood flow. Caudal flow in the ascending aorta in patients with normal aortic valve function may represent flow toward the coronary circulation. In patients with aortic insufficiency, this technique can be

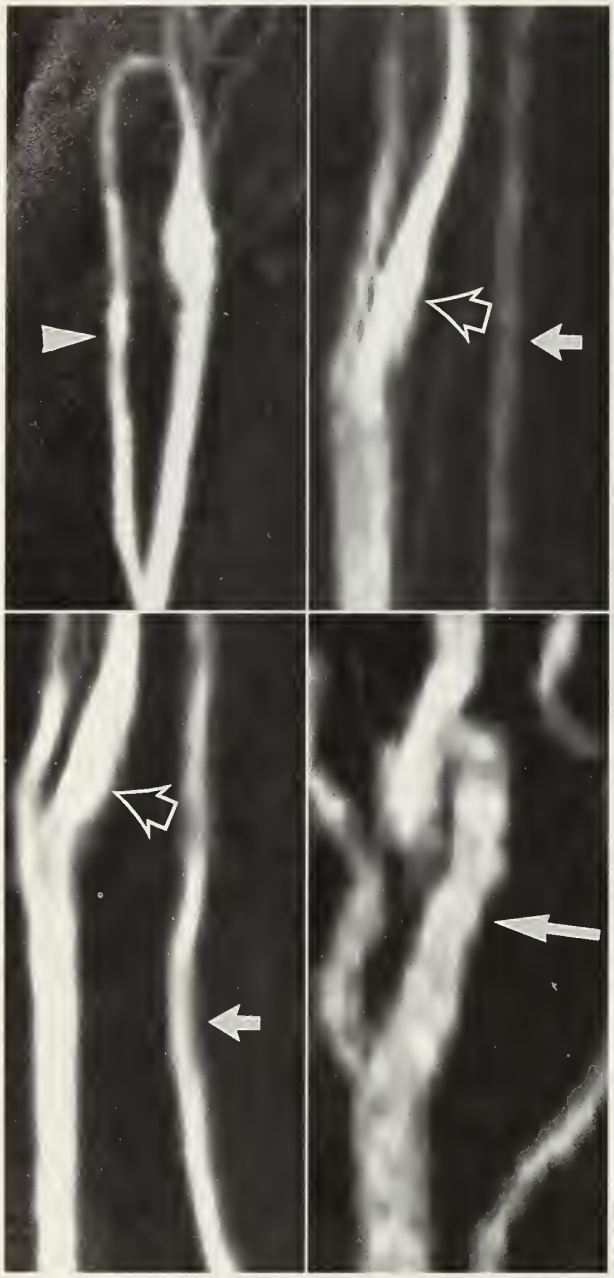

Figure 3.—A left dominant vertebral artery (**upper left, arrowhead**) is depicted in a frontal time-of-flight full-neck magnetic resonance angiography. Chosen lateral views of the volume of interest of the right (**upper right**) and left (**lower left**) common carotid bifurcations are compared with a right common carotid projection seen in a patient (**lower right**) with a folded right internal carotid artery (**long arrow**). Also shown are the internal carotid artery (**open arrows**) and the vertebral artery (**short arrows**).

used to directly measure the volumes of valvular regurgitation. Quantitative measurements may be useful for evaluating acquired and congenital lesions affecting pulmonary blood flow.[16] Cardiac output can be calculated easily by measuring the forward flow through the aorta. Cardiac shunts can also be evaluated by comparing left-sided cardiac output as measured at the aorta with the

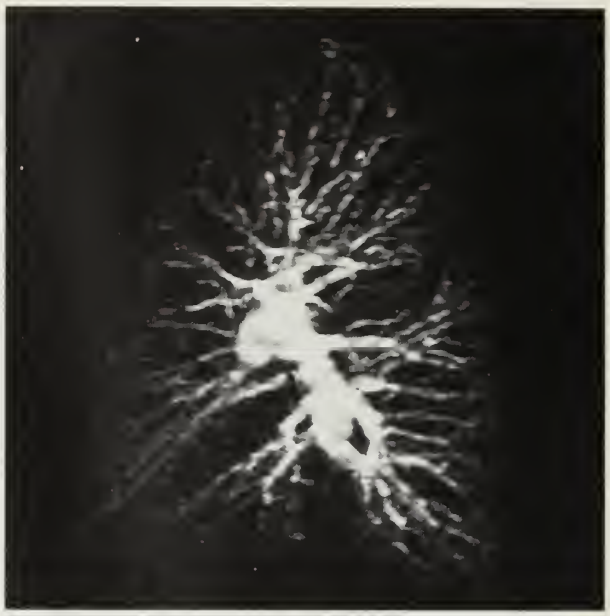

Figure 4.—A lateral view of a normal right lung from a magnetic resonance pulmonary angiogram was acquired with a time-of-flight technique in a healthy subject.

right-sided output as measured at the pulmonary artery.[17] These quantitative techniques (velocity-encoded cine MR) may prove useful in evaluating the severity of peripheral arterial stenoses because the normal triphasic flow pattern seen in peripheral arteries seems to become monophasic above and below hemodynamically important stenoses.[18]

Magnetic Resonance Angiography

A thorough evaluation of the cardiovascular system requires an evaluation of the blood vessels in addition to assessing patency and measuring flow. Conventional angiography has been the mainstay of such an evaluation. Over the past decade, however, MR angiographic techniques have been substantially improved, now allowing greater clinical use of this technique. Magnetic resonance angiography has several advantages over conventional angiography: noninvasiveness, no need for intravenous contrast (eliminating the risk of reactions), the potential of quantitative measurements, and the parenchymal information provided in addition to vascular anatomy.

Most published MR angiographic techniques use time-of-flight or phase-shift effects to produce signal from flowing blood within the blood vessels. Signal from surrounding static tissues is either suppressed or subtracted to increase the image of vascular detail. Vascular form and structure is then displayed in a projection format to simulate a conventional angiogram. With certain techniques, a rotating image is projected that can provide more information than a single or even two-plane conventional angiogram.[19]

Clinical Application

Magnetic resonance angiography was initially found to be useful in the head and neck because of technical advan-

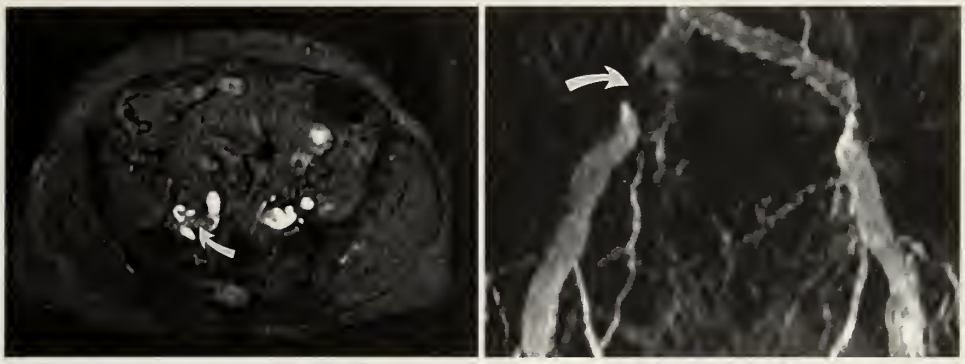

Figure 5.—An axial gradient-echo image **(left)** and a frontal view from a time-of-flight magnetic resonance venogram **(right)** show a focal thrombus **(arrows)** in the right iliac vein.

tages, including the lack of cardiac, respiratory, and peristaltic motion. The high incidence of atherosclerotic disease involving the surgically accessible carotid bifurcation has made the extracranial carotid circulation an area of concentrated research. Although the ability of MR angiography to quantitate carotid stenoses has steadily improved, the technique remains limited mainly due to signal loss from poststenotic turbulence and disturbed flow, such as that produced by intimal ulcerations. Magnetic resonance angiography, therefore, consistently overestimates the presence of stenoses, especially severe stenosis (Figure 2).[20-22]

The strengthened visualization of intracranial vascular anatomy has proved useful in searching for intracranial aneurysms. Of great value are selected "volumes of interest" that afford an interpreter several postprocessing image manipulations in three planes. Overlapping vessels may therefore be removed from the image, and the vascular tree may be positioned for optimal viewing of a specific portion of it. Magnetic resonance angiography may fail to detect the smallest aneurysms, but small aneurysms may not be at risk of rupture. This procedure, therefore, may be used predominantly as a screening tool in asymptomatic patients at risk for cerebral aneurysm. These may include patients with adult polycystic kidney disease, in whom a 10% to 15% incidence of berry aneurysms has been reported.[23,24] In a recent review, MR angiography was found to have a sensitivity of 95% and a specificity of 100%, compared with conventional angiography, for detecting intracranial aneurysms.[25] Patients with subarachnoid hemorrhage from possible aneurysmal rupture are primarily examined with conventional film angiography, which affords resolution currently unavailable with MR angiography (Figure 3).

Magnetic resonance angiography provides an evaluation for intracranial occlusive disease involving major arteries and veins. Such information is complementary to the sensitive evaluation for infarction provided by MR imaging.[26-29]

Intracranial MR angiography is of some value in characterizing the vascular supply of neoplasms and in observing arteriovenous malformations after surgical repair or embolization.[30]

Magnetic resonance angiography may also prove to be useful in planning for stereotactic biopsies and operations on the brain. The advantages of MR over other modalities include the ability to show both vasculature and soft tissue, its noninvasiveness, its high contrast with regard to delineating disease, and the potential of true three-dimensionality of data.[31]

The arteries in the thorax are pulsatile and are best evaluated with cardiac gated or cine techniques as described earlier. Magnetic resonance angiography can nevertheless be used to evaluate accurately the great vessels and veins of the thorax, including the superior vena cava. Magnetic resonance venography depicts central venous compression from adjacent masses as well as thrombosis with great accuracy.[32]

High-resolution images of the pulmonary arteries have also been obtained with MR angiography. Work is now going on to test these techniques in patients with pulmonary embolism (Figure 4).[33]

Magnetic resonance angiography and even conventional gradient-echo techniques are useful for evaluating abdominal vasculature. These techniques can confirm portal venous patency of the portal splenic and mesenteric circulation and determine the direction of flow. Portosystemic collaterals can be identified, and portosystemic shunts can be evaluated. Some centers now use MR angiography to evaluate patients before and after liver transplantation. Hepatic venous and caval patency can also be evaluated to exclude the Budd-Chiari syndrome. Magnetic resonance angiography can also document the relationship of liver tumors with the hepatic veins.[34]

Magnetic resonance angiography is sensitive to the presence of occlusive and nonocclusive thrombi in the renal veins and vena cava, making it of great value in the evaluation of renal cell carcinoma. It shows great promise for screening patients with hypertension for renal artery stenosis, with reported sensitivities as high as 100%. Limitations include an overestimation of the degree of stenosis, lessened sensitivity for the distal stenoses commonly seen with fibromuscular dysplasia, and the imperfect detection of small accessory renal arteries.[35-37]

So far, little work has been done on the use of MR angiography for evaluating peripheral arterial disease.[38,39] It has been used to evaluate runoff vessels in candidates for bypass operations. It was used to find all runoff vessels shown by conventional angiography, but found several

that conventional angiography failed to detect.[40] Certainly, MR angiography can play a role as a noninvasive screening technique for peripheral arteries and as an alternative to conventional angiography for long-term postintervention follow-up.

Magnetic resonance angiographic and gradient-echo techniques can be used for peripheral venography to detect the presence of thrombosis or extrinsic compression. Although ultrasonography is accurate for evaluating the veins in the thighs, MR angiography can also evaluate the deep veins in the pelvis and calves (Figure 5).[41,42]

Summary

Magnetic resonance imaging is a valuable tool for the noninvasive assessment of the cardiovascular system. Traditional spin-echo and rapid gradient-echo techniques have proved useful for obtaining images of blood flow and vessel patency. The phase-contrast MR flow examinations also provide two-dimensional instantaneous velocity and flow profiles with high temporal resolution. Blood flow dynamics are delineated better than with any other invasive or noninvasive method for examining flow. Furthermore, many vessels that are not accessible by other noninvasive methods can be examined, such as those contained within the calvarium. As techniques continue to improve, MR angiography will become more reliable and clinically useful throughout the body. Although conventional angiography is in no immediate danger of becoming obsolete, many invasive and costly examinations may be avoided with the use of MR angiography.

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Depression Followed by Dementia and Disordered Movement

Clinicopathologic Correlation

Discussants
CHERYL P. HARRIS, MD; JEANNETTE J. TOWNSEND, MD; *and* JOHN C. ADAIR, MD, *Salt Lake City, Utah*

Clinical History

JOHN C. ADAIR, MD*: A 62-year-old man was brought to the hospital by his wife in April 1989 for evaluation of a progressive decline of cognitive function. His spouse first noted problems three years previously: as she underwent and recovered from a complicated surgical procedure, her husband displayed uncharacteristic indifference toward her condition. He then became withdrawn and "lost his sense of humor." Job performance also deteriorated, leading to retirement within a year.

Evaluation in 1987 included psychometric tests that demonstrated impairment of auditory memory and geriatric depression scale scores indicating a moderately severe affective disorder. A cranial computed tomographic (CT) scan showed lucency of periventricular regions with mild cortical atrophy. Numerous blood tests showed normal values, including serum vitamin B_{12} and folic acid levels, thyroid studies, rapid plasma reagin, serum copper and ceruloplasmin levels, and an erythrocyte sedimentation rate. Clinicians judged that the primary process was major affective disorder and treated him with tricyclic antidepressants.

Despite therapy, the patient's cognitive abilities declined. In addition to worsening memory, tremulousness of his hands developed. He also suffered anxiety attacks and had disturbing sensations that compelled him to disrobe.

The patient's history was remarkable for mild hypertension, although he had not required treatment for five years. No other family members had either dementia or a movement disorder. He was a mining engineer, but his occupation had never brought him into contact with manganese or heavy metals.

The results of a general physical examination on hospital admission were unremarkable. Speech was hypophonic with occasional paraphasic errors. The Folstein Mini-Mental Status score was 18 of a possible 30; orientation was incomplete, recall was severely impaired, and he was incapable of writing sentences, copying figures, and performing serial subtraction tasks. Motor function showed diffuse atrophy without fasciculations and mild symmetric weakness in all extremities. A low-amplitude tremor was superimposed on upper extremity movements, but no dysmetria was observed. Gait was normal

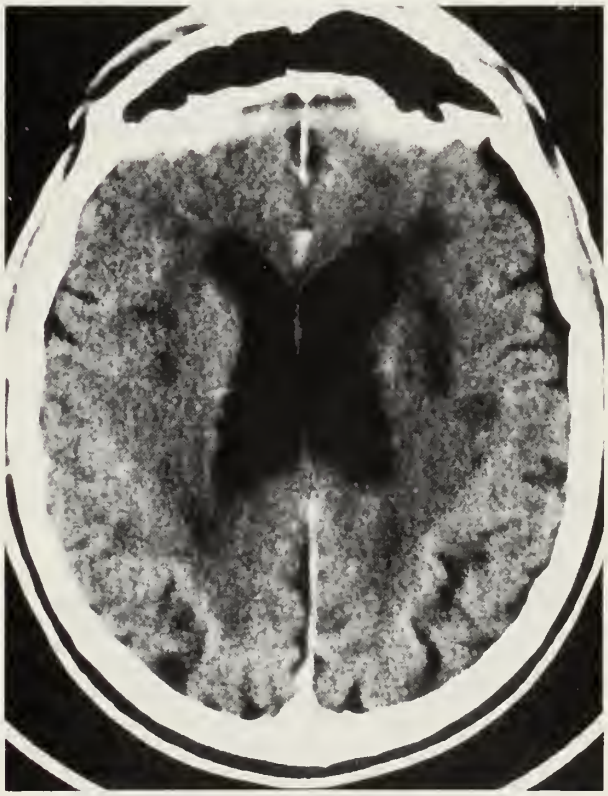

Figure 1.—An axial computed tomographic scan through the lateral ventricles shows mild cortical atrophy with *ex vacuo* ventricular dilatation and diffuse periventricular white matter disease.

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aside from a decreased right arm swing. Deep tendon reflexes were symmetric at 3+ in the upper extremities, 2+ at the knees, and 1+ at the ankles. Plantar responses were flexor. Abnormal reflexes included a palmomental sign, snout and grasp reflexes bilaterally, and an increased jaw jerk.

A cranial CT scan again showed diffuse atrophy and patchy periventricular hypodensity (Figure 1), interpreted by a radiologist as consistent with Binswanger's disease. An electroencephalogram displayed symmetric slowing of background rhythm without focal features. Spinal fluid examination revealed no erythrocytes, 1×10^9 leukocytes per liter (1 leukocyte per mm^3), a normal glucose level, and a protein content of 0.65 grams per liter (65 mg per dl). A working diagnosis of vascular dementia was established, and aspirin was added to the medication regimen.

Increasingly agitated behavior resulted in a therapeutic trial of low-dose haloperidol in the spring of 1990. Shortly thereafter, the patient was observed in clinic to have a shuffling gait and increased appendicular tone. Parkinsonian symptoms persisted despite discontinuation of the neuroleptic drug. Over the next three months, incontinence developed, and he became markedly less ambulatory. At the time of placement into an extended-care facility in July 1990, he was nearly mute and practically immobile, with extremities fixed in a flexion posture. He died of aspiration pneumonia following 11 months of institutional care, 5 years after the onset of his disease. Permission was obtained for an autopsy.

Discussion

Cheryl P. Harris, MD*: This man died with a dementing illness that spanned at least five years. When he was first seen, he had signs and symptoms thought to reflect an affective disorder, but cognitive loss soon supervened. A neurologic examination several years into the course of the disease revealed diminished higher cortical functions, symmetric motor weakness, a diffuse tremor, and cogwheel rigidity. The extrapyramidal signs persisted after a neuroleptic medication was stopped. A CT scan showed no focal processes, and spinal fluid evaluation was nondiagnostic.

The differential diagnosis of dementia in this patient's age group is expansive. In the evaluation of dementing illnesses, emphasis is rightfully placed on detecting reversible conditions. The results of several tests done to investigate such reversible diseases can help to narrow the diagnostic possibilities in this patient. Thyroid function was normal, as was a serum vitamin B_{12} level, making the diagnosis of dementia from either hypothyroidism or pernicious anemia untenable. The patient also had no history of substantial alcohol consumption, eliminating a possible alcohol-related disorder. Depression in older patients frequently is confused with dementia, and the results of psychological testing in this patient were suggestive of depression. Treatment with antidepressants, however, did not alleviate the symptoms, and the course of the illness and progressively severe cognitive decline are not consistent with depression. Clinically serious depression, though, may frequently coexist with many of the primary dementias.[1]

Another consideration in evaluating dementing diseases is the time course of various symptoms accompanying the illness. Paraneoplastic disorders, such as limbic encephalitis, may give rise to personality changes and memory disturbances[2] and should be considered in middle-aged patients. Lung cancer, particularly oat cell carcinoma, is the most common tumor underlying this condition. Although encephalopathy may be the presenting feature in this situation, an occult malignant neoplasm would have progressed to a symptomatic state over the five-year course of the patient's illness. Similarly, the diagnosis of Huntington's disease can be eliminated. Although personality alterations and failing intellect may precede the onset of the movement disorder by several years,[3] the classic choreiform movements eventually supervene.

The time course of the dementing illness itself may also serve to differentiate it from the others. The mean duration of disease in 45 patients with Creutzfeldt-Jakob disease was 11.5 months, with some of the patients surviving only 3 months after the start of their illness.[4] Other factors that do not favor the diagnosis of Creutzfeldt-Jakob disease in this patient include the lack of startle myoclonus, which is frequently described in patients with this disease, and an electroencephalogram that showed symmetric slowing but not the classic pattern of "burst suppression" commonly seen in this disorder.[4]

The dementia complex associated with the acquired immunodeficiency syndrome is defined by disabling cognitive impairment usually accompanied by motor dysfunction, behavioral change, or both.[5] There are a number of reasons why this diagnosis is not appropriate in the patient under discussion. No risk factors for human immunodeficiency virus infection are mentioned in the clinical record. The serologic test for human immunodeficiency virus antibodies is not mentioned, perhaps because it was not done. As alluded to previously, a five-year illness duration without other systemic signs of the acquired immunodeficiency syndrome would be distinctly unusual.

Another category of diseases to consider in this patient includes the vascular dementias. Some authors think that multiple cerebral infarcts are the second most common cause of dementia after Alzheimer's disease.[6] The clinical history generally described with multiple infarct dementia is an abrupt occurrence of focal neurologic symptoms and a stepwise deterioration of neurologic function.[7] In addition, the strokes should be visible on neuroimaging studies. None of these characteristics are described in this patient.

Serious consideration needs to be given to the diagnosis of Binswanger's disease (subacute arteriosclerotic encephalopathy). In 1894, Binswanger described cases of "slow progression of mental deterioration" and white

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matter disease in patients with chronic hypertension.[6] These patients have a spectrum of symptoms, and some may even be asymptomatic.[8] The most commonly described symptoms include gait apraxias, motor dysfunction, urinary incontinence, and pseudobulbar palsies.[9] Although the patient presented here is described as having diffuse symmetric weakness, pseudobulbar signs are not mentioned, and incontinence developed late in the course of his disease. In addition, although he apparently did have high blood pressure in the past, the hypertension was thought to be quiescent and required no medical treatment for some time before he was seen. A CT scan of the brain in our patient showed periventricular lucencies, and the radiographic picture suggested Binswanger's disease to the radiologist. Hachinski and co-workers coined the term "leukoaraiosis" to describe this periventricular leukomalacia,[10] a term that may or may not be synonymous with Binswanger's disease. Although the imaging study is consistent with this diagnosis, the clinical findings and the absence of chronic uncontrolled or poorly controlled hypertension argue against a diagnosis of Binswanger's disease.

Another less common cause of dementia in elderly persons is progressive supranuclear palsy. The cardinal feature of this dementia, in addition to a progressive dementia and extrapyramidal signs, is a supranuclear ophthalmoplegia primarily limiting vertical gaze.[11] Although the patient did have a tremor (which may occur in progressive supranuclear palsy), the eye movements were described as being normal and apparently remained so throughout the course of the patient's illness. This is not compatible with the diagnosis of progressive supranuclear palsy.

The most common primary dementia in the United States is Alzheimer's disease. The cause of this disease is unknown, but evidence of a genetic predisposition is mounting.[3] The definitive diagnosis of Alzheimer's disease requires a neuropathologic examination,[12] but several neurologic signs and symptoms point towards this diagnosis. In addition to cognitive decline, speech disturbances are common initial findings.[13] These include repeating words or phrases (echolalia), dysnomia (especially for proper nouns), and problems in understanding written or oral speech. Various motor apraxias may be seen early in the course of the disease, and frequently visuospatial dysfunction is present. Extrapyramidal signs such as tremor and increased motor tone are uncommon early in the disease course but may appear as the illness progresses.[3] As there are no clinical or biochemical criteria that are diagnostic of Alzheimer's disease before death, the condition cannot be definitely excluded in the patient under discussion. History obtained from the patient's wife, however, does not seem to indicate a prominent speech disorder or a loss of motor skills early in the illness course, but rather a diffuse personality change and memory loss. The duration of Alzheimer's disease is usually between four and ten years,[13] and the five-year period of illness of our patient falls into this range.

Another uncommon form of primary dementia is Pick's disease (lobar sclerosis). Although the clinical findings in this condition are not specific, the disease can be differentiated pathologically from other dementing illnesses. Clinical features frequently described with Pick's disease include signs of temporal lobe or limbic system origin, including lapses in social conduct, disinhibition, bulimia, and gluttony.[14] In addition, radiologic imaging studies show, as the name of the condition implies, lobar atrophy more prominent in either or both the frontal or temporal poles than that which is seen in Alzheimer's disease.[15] Although it cannot entirely be discarded as a possible diagnosis, none of these features were prominent in the patient under discussion, and Pick's disease is unlikely.

A final class of dementing illnesses to consider includes two conditions that are perhaps linked more by their histologic findings than their clinical aspects: Parkinson's disease and diffuse Lewy body disease. The clinical features of idiopathic Parkinson's disease are familiar to physicians—bradykinesia with rigidity, resting tremor, and a loss of the postural reflex.[16] The cognitive capacity of patients with Parkinson's disease remains a controversial issue. Reports range from the initial one by James Parkinson, who was of the opinion that intellectual function was unaffected in these patients,[16] to an estimate that substantial dementia occurs in 20% to 40% of patients.[17] Patients with this disorder initially show a movement disorder, and dementia appears in the later stages of the disease, if at all. Although this patient had a low-amplitude tremor and an increase in tone on examination, his decline in cognitive function clearly predated and surpassed any extrapyramidal signs.

Lewy bodies, the pathologic hallmark of Parkinson's disease, were first described in 1912 by Lewy[18] and were found primarily in pigmented neurons of the brain stem. In 1961, however, Okazaki and associates described the presence of Lewy bodies in the medium-sized neurons of the cerebral cortices in patients with dementia.[19] In time, diffuse Lewy body disease, as this condition is now called, has become recognized as a separate clinicopathologic disorder from Parkinson's disease. Diffuse Lewy body disease is thought to occur more frequently in men than in women,[18] and the mean age of onset in a report of 15 patients was 72 years.[20] In a review of autopsy results of 216 demented persons, diffuse Lewy body disease was the second most prevalent disorder, outranked only by Alzheimer's disease.[21] Unlike some of the other primary dementias, no distinct genetic patterns have been found to suggest a familial tendency to the condition.[22]Although the disease is still not commonly diagnosed before death, some authors think that it encompasses clinical features unique enough to differentiate it from other primary causes of dementia. These features include psychiatric symptoms, impaired gait, abnormalities in tone, and resting tremor and were prominent early symptoms in some patients.[21] Extrapyramidal signs are usually overshadowed by dementia, however,[18] in contrast to Parkinson's disease. To further cloud the clinical differentiation of dementias, there have been reports of patients with suffi-

cient pathologic criteria for both diffuse Lewy body disease and Alzheimer's disease.[22]

The course of the illness of this patient is most consistent with the clinical history of diffuse Lewy body disease, with prominent dementia but underlying cogwheel rigidity, tremor, and a shuffling gait. Evaluation of this man's extrapyramidal symptoms is complicated by his being given haloperidol, which is well known to induce parkinsonian symptoms. The presence of tremor before the medication's administration and the persistence of tremor and cogwheel rigidity after the drug's withdrawal would seem to indicate a primary bradykinesia rather than secondary extrapyramidal effects. Although other dementing illnesses cannot be excluded with certainty, diffuse Lewy body disease is the most likely diagnosis.

Neuropathologic Examination

JEANNETTE J. TOWNSEND, MD*: The general autopsy revealed that an aspiration pneumonia was the cause of death.

On neuropathologic examination, the brain weighed 1,375 grams and showed minimal frontal atrophy. Mild dilatation of the lateral ventricles was evident on coronal sections with no identifiable focal lesions (Figure 2). Pallor of the substantia nigra was the only grossly visible abnormality on axial sections of the brain stem. The cerebellar hemispheres were normal. Mild atherosclerosis of the right posterior cerebral and left middle cerebral arteries was found.

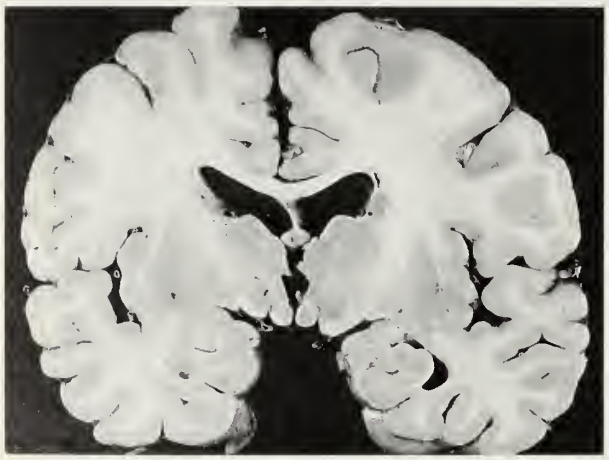

Figure 2.—A coronal section of the brain shows minimal atrophy with mild *ex vacuo* dilatation of the lateral ventricles.

Histologic sections of the substantia nigra revealed a loss of pigmented neurons with incontinence of melanin pigment. Numerous intracytoplasmic, rounded, pink inclusions (Lewy bodies) were found in the remaining neurons (Figure 3). Similar Lewy bodies, although less distinct, were present throughout the frontal and parietal cortices (Figure 4, top). These Lewy bodies reacted positively with monoclonal antibodies to ubiquitin (Figure 4, bottom). Neither senile plaques nor neurofibrillary tangles were identified in the hippocampus or cortex. No vascular or white matter changes were found to suggest Binswanger's disease.

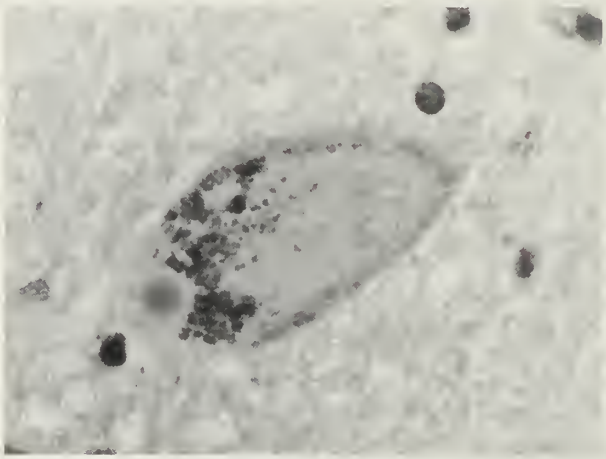

Figure 3.—A round eosinophilic Lewy body with a surrounding halo is seen in a pigmented neuron of the substantia nigra (hematoxylin and eosin stain, original magnification × 800).

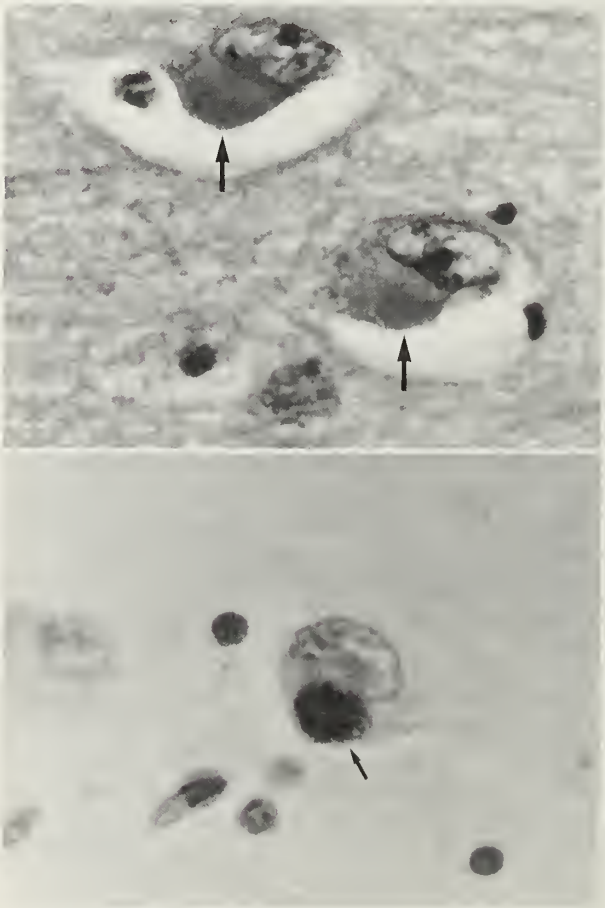

Figure 4.—Top, Two small cortical neurons are depicted with cytoplasmic ill-defined Lewy bodies (arrows) (hematoxylin and eosin stain, original magnification × 800). Bottom, Immunohistochemical staining with the antibody to ubiquitin shows a positive reaction in an intracytoplasmic Lewy body (arrow) (peroxidase stain, original magnification × 800).

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These findings are typical of diffuse Lewy body disease. At autopsy, these patients usually show only minimal atrophy of the cerebral hemispheres with pallor of the substantia nigra and locus ceruleus. On histologic examination, patients with diffuse Lewy body disease show neuronal loss and pigmentary incontinence in the substantia nigra with intracytoplasmic Lewy bodies.[18] Lewy bodies are also found in many other areas of the brain stem and basal ganglia, including the locus ceruleus, dorsal motor nucleus of the vagus nerve, and the substantia innominata. Within the small or medium-sized neurons of the deeper cortical layers, similar intracytoplasmic inclusions are found. They are not as distinct as those in the pigmented neurons but tend to be ill-defined and paler without a surrounding clear halo.[18] Almost any area of the cortex may contain Lewy bodies, but the parahippocampal, anterior temporal, and cingulate gyri are more frequently affected. The average number of cortical Lewy bodies ranged from 10 to 12 per section of cortex examined by one group of researchers.[23] Immunohistochemical staining with antiubiquitin, which is a polypeptide involved in an adenosine triphosphate-dependent breakdown of abnormal cellular proteins,[22] is strikingly positive and usually demonstrates many Lewy bodies that are not seen with hematoxylin and eosin stains. By electron microscopy, Lewy bodies are composed of filamentous and granular material with a halo formed of filaments around a dense core. The cortical Lewy bodies are similar but lack the filamentous halo.[18]

Many patients with diffuse Lewy body disease are misdiagnosed clinically with Alzheimer's disease because of the pronounced dementia that occurs during the course of the disease. The bradykinesia and other symptoms of parkinsonism that these patients may exhibit should alert clinicians to the possibility of diffuse Lewy body disease. In some instances, pathologic changes of both Alzheimer's disease and diffuse Lewy body disease are found in the same patient: these patients have been described as having the "Lewy body variant" of Alzheimer's disease.[22]

An increasing number of cases have been recognized over the past 30 years since the first case of diffuse Lewy body disease was reported.[19] As the cortical Lewy bodies may be difficult to see, they can easily be missed on a standard hematoxylin-eosin stain. Immunohistochemistry for ubiquitin is warranted in any case in which there is a clinical diagnosis of dementia and Lewy bodies are found at autopsy within the substantia nigra.

Acknowledgment

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Epitomes

Important Advances in Clinical Medicine

Internal Medicine

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in internal medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Thyroid Function Tests—The Next Generation

THYROID FUNCTION TESTS have improved in sensitivity and reliability during the past few years, but can be bewildering. Measuring serum levels of thyroid-stimulating hormone (TSH) has become one of the most important tools in the diagnosis of thyroid disorders since its introduction in 1964. Several generations of tests are available. With the first-generation TSH assay (sensitivity of 1 mU per liter), clinicians were able to identify the presence of hypothyroidism, but could not differentiate between persons with normal thyroids and those with hyperthyroidism. This has now been replaced by second- and third-generation assays (also referred to as sensitive and ultrasensitive). Each new generation represents a tenfold improvement in sensitivity (second-generation sensitivity of 0.1 mU per liter, third-generation sensitivity of 0.01 mU per liter). Enhanced sensitivity provides the advantage of distinguishing marginal TSH suppression, seen with subclinical hyperthyroidism and some nonthyroid illnesses, from the profound reduction found in thyrotoxicosis (<0.005 mU per liter). The newer TSH assays also have the technical advantage of a turnaround time of less than three hours.

At present, thyroid specialists agree that measuring serum TSH levels using second- and third-generation methods, complemented by a free thyroxine (T_4) estimate, is the best combination of blood tests for the diagnosis and follow-up of most thyroid disorders. There is, however, a trend to replace a combination of tests by a single discriminating thyroid assay, reflecting an increased awareness of cost-effectiveness and technical improvement. For example, one recommended cost-effective strategy is to use a third-generation TSH screening value of less than 0.05 mU per liter to alert a physician to direct the laboratory to do a free T_4 test if the patient is taking thyroid preparations or to measure both free triiodothyronine and T_4 levels if the patient is not taking thyroid preparations.

These newer TSH assays of thyroid function may be used as a single test when screening for primary thyroid dysfunction in ambulatory patients. Testing should be directed toward patients with suspected thyroid diseases and in certain high-risk populations, such as newborns, those with a strong family history, patients aged 65 or older, women four to eight weeks' postpartum, patients with autoimmune disease, such as Addison's disease and type I diabetes mellitus, and patients with hypercholesterolemia. As a screening test, either pronounced elevations (>20 mU per liter) or depression (<0.01 mU per liter using a third-generation assay) is highly suggestive of thyroid dysfunction.

In contrast, most patients with nonthyroidal illness have only marginal abnormalities in serum TSH values. Other applicable settings include patients with newly diagnosed goitrous disease, patients with hypothyroidism, those with a history of treatment of hyperthyroidism, and patients receiving thyroid hormone replacement or suppressive therapy. The use of the serum TSH assay for monitoring thyroid hormone replacement therapy allows treatment to be "fine tuned," avoiding subtle overtreatment or undertreatment. A minimum of eight weeks should be allowed after adjusting the thyroid hormone dosage before retesting, to assure a new steady state has been reached. The goal is to return TSH values to within the normal range. Annual serum TSH determinations are satisfactory for follow-up. In conditions warranting thyroid hormone suppressive therapy, such as thyroid cancer or goitrous disease, the goal is to reduce serum TSH levels to the subnormal range (<0.1 mU per liter).

The TSH assay is not recommended as a single first-line test in patients with clinical hyperthyroidism, patients receiving therapy for hyperthyroidism, or patients with known or suspected hypothalamic or pituitary disease. It is also not recommended as a sole screening test for sus-

pected thyroid disease in the presence of severe nonthyroidal illness.

It is important to remember that TSH and free T_4 levels provide complementary information regarding the normality of thyroid T_4 production and biologic action. Thyroid-stimulating hormone assays serve as the most sensitive and specific indicators of the biologic effects of circulating hormone, but free T_4 estimates only measure the T_4 secretory activity of the thyroid gland. Widespread clinical use of the next generation of TSH assays (for example, the fourth generation) appears to be on the horizon.

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Watchful Waiting for Localized Prostate Cancer

THE WIDE APPLICATION OF new detection methods—serum prostate-specific antigen, transrectal ultrasonography, and systematic prostate biopsy—has made carcinoma of the prostate the most commonly detected cancer in American men. Most prostate cancers are localized, and with some exceptions, these are treated in the United States. Early detection and treatment, however, may have no effect on cancer-specific mortality. Although the rate of radical prostatectomy for patients aged 65 to 79 has increased by a factor of 5 since 1984, and a similar increase in irradiation has undoubtedly occurred, treatment does not guarantee freedom from eventual metastases and may have an adverse effect on the quality of life.

Given the uncertainty about the best treatment of localized prostate cancer and the fact that the protracted course of the cancer in an aging patient may render treatment unnecessary, several physicians have questioned its usefulness. In selected series of patients in whom therapy was deferred, reported progression rates ranged from 34% to 67%, but prostate cancer was the cause of death in 5% to 16%. Many such series are composed largely of patients who are older, have well-differentiated cancers, and may have concurrent medical diseases. Therefore, they may not represent well the general population of patients with prostate cancer. Progression and cause-specific mortality rates are related to tumor stage and grade. Many suggest that trials designed to demonstrate the efficacy of treatment should include untreated controls for comparison and carefully document several important clinical end points: survival, cause-specific survival, and progression-free survival.

Recognizing that the efficacy of treatment has not been demonstrated and that different treatments may be associated with different risks and changes in a patient's quality of life, the Prostate Patient Outcomes Research Team constructed a decision analysis to compare the results of watchful waiting with those of either radical prostatectomy or external-beam irradiation in men with localized prostate cancer (clinical stages T0 to T2). Possible benefits (decreased mortality or disuse from metastatic disease) and risks (treatment-related morbidity and mortality) were based on a literature review and were included in the model to analyze expected outcomes based on tumor grade and state of health for men aged 60 to 75. Although aggressive treatment conferred a marginal survival advantage in men younger than 70, quality-adjusted life expectancy improved only in younger patients with higher-grade cancers. Men 75 years and older were not likely to benefit from treatment. The benefit was sensitive to assigned utility values or probabilities for different outcomes—incontinence, impotence, or the development of metastases—underscoring the need to inform patients fully. Although constructing the model from the literature carried inherent limitations (patient populations may be incompletely described, staging can vary, and the rates of complication, recurrence, and progression may be poorly reported), one can infer that benefit of treating localized prostate cancer has not been well documented.

Older or infirm patients with well-differentiated cancers may not benefit from aggressive treatment and are, therefore, good candidates for watchful waiting. Patients with higher grade cancers, however, are at substantial risk of disease progression and should be offered potentially curative treatment. Tumor grade and stage are the guiding factors, but even tumors of similar grade and stage may be associated with vastly different clinical results. Current research of considerable importance is examining whether certain phenotypic—such as proliferation or angiogenesis—or genetic features of individual cancers provide a more accurate assessment of risk.

It is not clear how patients who choose watchful waiting should best be observed, and suitable end points for intervention have not yet been established. Although newly detected cancers may be associated with a protracted natural history, patients should be told of the possibility of progression and that the treatment of metastatic disease is palliative. They should be informed of all treatment options, and the likelihood of different outcomes should be included in any discussion of the treatment of localized prostate cancer.

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Screening for Prostate Cancer

SCREENING FOR PROSTATE CANCER is an attempt to detect the disease in patients who are asymptomatic. Because local treatments (surgery or irradiation) can cure organ-confined disease, many physicians and patients feel that early detection will lead to improved overall survival. Prostate cancer screening, however, has not been proved to be beneficial. The possible harms of screening include applying treatment (together with the side effects) to patients who would not suffer ill effects from their cancer during their lifetime. This includes men in whom the natural history of their prostate cancer will not match that of their other diseases or advanced age. It also includes younger healthier men with "biologically insignificant" tumors. To justify screening programs, we must avoid detecting biologically insignificant cancers and detect and effectively treat asymptomatic cancers that would otherwise progress and cause illness or death.

The results of digital rectal examinations are abnormal in 3% to 15% of screened men, leading to biopsies that reveal cancer in 0.2% to 3%. Because 30% of men older than 50 years have prostate cancer (by autopsy studies), digital rectal examination is not a good screening tool. On the other hand, for a patient in a physician's office for any reason whatsoever, this examination is relatively noninvasive, inexpensive, and has possible benefits unrelated to prostatic disease.

Transrectal ultrasonography is more invasive, expensive, not widely available, and suffers from a lack of findings specific to prostate cancer. It is interpreted as abnormal in 7% to 60% of studies, resulting in the identification of tumors in 2% to 20% of the original group. These numbers suggest that transrectal ultrasonography would detect a higher number of cancers than would digital rectal examination, but too many men would be subjected to a biopsy with negative results. Because of these reasons, transrectal ultrasonography is not recommended as a screening procedure.

Transrectal ultrasonography has become a useful way of accurately directing multiple systematic quadrant- or sextant-type biopsies throughout the gland (regardless of the echo pattern) after another test indicates that a biopsy be done. If hypoechoic lesions are seen, biopsies may also be taken of them. Whereas transrectal ultrasonography certainly has other roles in the management of patients with known prostate cancer, for screening it has become merely a tool to assist in biopsy.

Serum prostate-specific antigen (PSA) measurement is now being used as a screening tool. A large number of patients with elevated PSA levels do not have cancer, however. Also, many patients with localized, asymptomatic prostate cancer do not have an elevated PSA level. If PSA levels are used to screen asymptomatic patients, a threshold must be defined for referral for biopsy. A lower threshold will result in more cancers detected but will also lead to a higher number of unnecessary biopsies. Many series in the literature use a PSA level as part of a multiple-test screening protocol. Only a few studies use a PSA level as the initial screening tool; these studies are most analogous to the everyday situation of physicians ordering PSA levels on patients without prostatic symptoms. One study reported a positive test rate of 15% and 3% for PSA thresholds of 4.0 and 10.0 μg per liter (Hybritech monoclonal units). Their cancer detection rate was 30% and 50%, respectively, in the men who underwent a biopsy. This represented 2.5% and 0.7% of the original number of men screened. Although systematic ultrasound-guided sextant biopsies were recommended for every man with a PSA level higher than 4.0 μg per liter, only 56% consented to the procedure. Making a correction for the men who refused a biopsy, the cancer detection rate would be about 4.5% and 1.5%, respectively, for the two threshold levels. These studies have since been repeated and the results confirmed by others.

At present, there is no consensus among urologists as to the indications for biopsy and whether or not to do systematic quadrant- or sextant-type biopsies. For example, an elevated PSA level above an arbitrarily set threshold will prompt some urologists to perform quadrant or sextant transrectal ultrasonogram-guided biopsies even if the results of the digital rectal examination are normal. On the other hand, other urologists will perform a biopsy only if a hypoechoic lesion is seen on a transrectal ultrasonogram or if there is palpable induration or a nodule.

Although serum PSA measurements will pick up more cancers than the digital rectal examination, each test will pick up some cancers that the other will miss. For this and other reasons, PSA measurement should not replace rectal examination in primary physicians' office practices. If screening is chosen, transrectal ultrasonography should be used only as a biopsy tool, not as a screening instrument.

Finally, it must be emphasized that there is no proven benefit of screening. At this time, there are no data to indicate that screening reduces the morbidity or mortality of prostate cancer. Screening may result in men receiving treatment unnecessarily due to either their coexistent disease, advanced age, or the indolent nature of the tumor itself. These men will suffer the morbidity and mortality of treatment without benefit.

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Diabetes Mellitus—New Hope for an Old Disease

DIABETES MELLITUS has been described since the age of the Egyptian pharaohs. We now recognize this disease to be much more than just hyperglycemia; rather, it is a com-

plex and heterogeneous metabolic disorder of absolute or relative insulin deficiency, causing microvascular and macrovascular disease with subsequent serious end-organ complications.

Until recently, convincing evidence documenting benefits in preventing diabetic complications by the tight control of diabetes was lacking. Results from two well-designed long-term studies, the Diabetes Control and Complications Trial and the Stockholm Diabetes Intervention Study, now show that intensified insulin treatment of patients with type I or insulin-dependent diabetes mellitus (IDDM) leads to a substantially reduced frequency of retinopathy, nephropathy, and neuropathy. These studies showed a dramatic reduction of most diabetic complications in the range of 30% to 60% by using intensified insulin treatment. Although specialized diabetic centers that have the appropriate multidisciplinary support team are generally more successful in implementing intensified treatment, appropriately trained and motivated primary care physicians should be able to achieve comparable results.

The intensified treatment regimen of insulin includes keeping the fasting and premeal serum glucose levels between 4.4 and 6.7 mmol per liter (80 and 120 mg per dl) and the two-hour postprandial serum glucose level under 10.0 mmol per liter (180 mg per dl). The glycosylated hemoglobin should be kept within 10% of the upper limit of the normal range. To avoid hypoglycemia, serum glucose levels should be maintained at or above 3.0 mmol per liter (55 mg per dl). Continuous subcutaneous insulin infusions or more frequent insulin injections are required to achieve this control. The short-acting insulin can be given just before each meal and the intermediate-acting insulin given at bedtime—resulting in three to four insulin injections per day compared with the more conventional one to two injections. The yearly cost of intensified insulin treatment has been estimated to be twice that of standard therapy, but the potential cost savings from preventing diabetic complications are immense.

Based on these more recent findings, it is now generally conceded that intensified insulin treatment is indicated in pregnant women with diabetes, patients with newly diagnosed IDDM, patients with uncomplicated IDDM with a life expectancy greater than ten years, and children. Intensified insulin treatment is contraindicated in patients with unstable proliferative retinopathy, advanced nephropathy (that is, unmistakable proteinuria), a life expectancy of less than ten years, an inability to self-monitor adequately, severe recurrent hypoglycemia or hypoglycemia without warning, coronary artery or cerebrovascular disease, and those who are noncompliant.

Controversy still exists concerning the efficacy of intensive hypoglycemic therapy (by insulin or oral sulfonylurea agents) in patients with type II or non-insulin-dependent diabetes mellitus (NIDDM). Caution should be used in extrapolating from studies designed for patients with IDDM, particularly with regard to the possible atherogenic complications arising from the hyperinsulinemic states observed in patients with NIDDM. Proper diet, exercise, and weight reduction still remain the cornerstone treatment methods for patients with NIDDM. In addition, for all patients with diabetes (both type I and type II), aggressive treatment of hypertension, especially using the angiotensin-converting enzyme inhibitors, has been shown to delay or prevent nephropathy, and laser photocoagulation has been successful in substantially reducing the incidence of blindness due to diabetic retinopathy.

Clearly in selected patients with IDDM, early intervention and intensified insulin treatment will substantially decrease the incidence of diabetic complications and should be implemented if at all possible. In fact, any important reduction in the levels of glycosylated hemoglobin will benefit patients with IDDM—whether or not euglycemia is reached. Because there is now clear evidence of effective preventive therapies, clinicians should revive their efforts in appropriately treating their patients. Patients with diabetes now have reason to be more optimistic about their future, which should be increasingly free from many of the devastating complications of diabetes mellitus.

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Pharmacologic Stress Echocardiography

NUMEROUS NONEXERCISE METHODS have been developed to evaluate ischemic heart disease in patients who are unable to achieve an adequate heart rate and blood pressure response with exercise. Most tests use pharmacologic agents such as dipyridamole, adenosine, or dobutamine to induce ischemia. Ischemia can be detected by electrocardiography (ECG), nuclear perfusion scans, or echocardiography. The accuracy of ECG changes alone is limited. Adding nuclear imaging improves accuracy but is expensive and time-consuming. Recent literature has suggested that a combination of dobutamine and two-dimensional echocardiography is a reasonable and economical alternative for detecting and evaluating coronary artery disease.

Dobutamine is a sympathomimetic amine that has primarily a β_1 effect. At low infusion doses (<10 μg per kg per minute), dobutamine has a predominant inotropic effect. Doses greater than 10 μg per kg per minute can also cause substantial tachycardia. Hence, dobutamine increases myocardial oxygen demand by causing an increase in contractility and heart rate. In the presence of coronary artery stenosis, myocardial oxygen supply fails to increase sufficiently, and ischemia is produced. Dobutamine stress echocardiography incorporates the use

of two-dimensional echocardiographic wall-motion analysis at baseline and during increments of intravenous dobutamine infusion. If an adequate chronotropic response (heart rate ≥ 85% of predicted maximum) is not achieved, small aliquots of atropine sulfate are administered intravenously to augment the heart rate further. Heart rate, echocardiographic images, blood pressure, and an ECG are recorded at the end of each stage. Myocardial ischemia is detected if substantial ST segment changes develop or a regional wall-motion abnormality is seen on two-dimensional echocardiography. Interpretation of stress echocardiography studies has been further enhanced by digital technology, which displays the images side by side for easy comparison. Diagnostic studies can be obtained in most patients, but may be limited by inadequate images or adverse side effects.

The specificity and sensitivity of detecting the presence of coronary artery disease by dobutamine stress echocardiography are comparable to exercise-stress nuclear studies when done by experienced laboratory technicians. The overall sensitivity and specificity of detecting coronary artery disease in patients with normal resting regional wall motion are 87% and 91%, respectively. The sensitivity increases to 97% in patients with multiple vessel disease. By localizing the region of inducible myocardial abnormalities, two-dimensional echocardiography can also identify a stenosed major coronary artery.

Dobutamine stress echocardiography has been used in evaluating patients after myocardial infarction for the detection of residual viable myocardium. Immediately after a prolonged ischemic insult, it is important to distinguish between necrotic and stunned but viable myocardium. This question becomes important clinically in determining the need for revascularization procedures. Low-dose dobutamine (5 to 10 μg per kg per minute) improves regional myocardial function in the area of viable myocardium but not in an area of myocardial necrosis.

The noninvasive detection of multivessel coronary artery disease and residual jeopardized myocardium is essential after myocardial infarction. If the patient has multivessel disease, dobutamine stress echocardiography will show a regional wall-motion abnormality in an area remote to the primary infarct site. Substantial residual stenosis in an infarct-related artery results in worsening of the preexisting regional myocardial abnormality. In addition, patients with an abnormal dobutamine stress echocardiogram after myocardial infarction have a higher incidence of future cardiac events compared with those who had a normal study.

Dobutamine stress echocardiography can be used to stratify the degree of risk in patients who are referred for a noncardiac vascular surgical procedure. The absence of an inducible new wall-motion abnormality with dobutamine stress echocardiography is an excellent negative predictor for postoperative cardiac events. A positive test, however, does not necessarily predict the development of postoperative cardiac complications.

The safety of dobutamine stress echocardiography has been shown in a large series of patients. Noncardiac side effects are usually minor and include nausea, anxiety, headache, and tremor. Cardiac side effects such as angina and supraventricular and ventricular arrhythmias do occur, but are usually well-tolerated and rarely require treatment. In more than 1,000 patients who have had dobutamine stress echocardiography, serious complications from myocardial ischemia did not occur. Symptomatic ischemia or arrhythmias were effectively treated with test termination, sublingual nitroglycerin, or short-acting β-blocker drugs.

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Tuberculosis and Human Immunodeficiency Virus Disease

THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) epidemic has exposed persons with the human immunodeficiency virus (HIV) and those who care for them to new dangers from an old pathogen, tuberculosis. Individual and public health risk can be reduced by conscientious adherence to reasonable exposure precautions, early screening, and informed selection of antituberculous regimens to treat both exposure and active disease.

It is estimated that 3 million people worldwide are infected with both *Mycobacterium tuberculosis* and HIV. In the United States, 5% to 10% of the 1 million persons infected with HIV are also infected with *M tuberculosis*. This rate is probably higher in areas with large homeless, injection drug using, or immigrant groups. The increasing incidence of tuberculosis (TB) in the United States since 1984 is generally attributed to cases associated with the AIDS epidemic. Further, in recent outbreaks on the East Coast, 96% of cases of multidrug-resistant TB occurred in HIV-infected persons. Unlike most opportunistic pathogens, *M tuberculosis* is contagious and causes potentially serious illness in immunocompetent as well as immunocompromised hosts.

Nosocomial transmission of tuberculosis to both staff and patients has been well documented. Of particular concern is the transmission of TB or multidrug-resistant TB (infection with *M tuberculosis* resistant to both isoniazid and rifampin) to patients and health care workers with HIV. Tuberculosis in HIV-infected hosts rapidly progresses, disseminating to extrapulmonary sites in as many as 70% of patients. DNA analysis of *M tuberculosis* organisms has shown that primary TB developed within five months of exposure in 37% of HIV-infected persons exposed to a source patient, compared with the 2% to 4% of immunocompetent contacts in whom TB develops within a year of exposure. Of patients with advanced HIV dis-

ease who are infected with *M tuberculosis* by such exposure, progression to active disease is expected in virtually all patients in the absence of prophylaxis.

Multidrug-resistant TB in non-HIV-infected patients is associated with high mortality, long hospital stays, and frequently failure of even the best available treatments. Patients with multidrug-resistant TB may remain infectious for several months after treatment is initiated, and the risk to staff is increased accordingly. In HIV-infected patients, multidrug-resistant TB can be devastating, with death occurring a median of one to four months after diagnosis. Multidrug-resistant strains usually develop through selection during the treatment of TB. In HIV infection, however, multidrug-resistant TB has also been shown to result from infection with exogenous drug-resistant strains of *M tuberculosis*, which can occur even during therapy for drug-susceptible TB. These recent data, and the guarded prospects for new therapies for either HIV infection or TB in the near future, show the importance of preventing exposure to TB, aggressive screening, and secondary prophylaxis of exposed persons.

Patients at high risk for tuberculosis—including injection drug users, homeless persons, incarcerated persons, immigrants from TB-endemic areas, and contacts of persons with infectious TB—presenting with cough or other respiratory symptoms should be placed on respiratory precautions until TB is excluded by three sputum specimens negative for *M tuberculosis* on acid-fast bacilli staining or another diagnosis is established that fully explains the patient's presentation. Even in the latter situation, it is prudent to document at least one negative sputum smear on acid-fast bacilli staining. In the hospital, respiratory precautions include private, negative-pressure rooms with at least six room-air changes per hour and no recirculation of air into the rest of the building. Masks to filter out 1-μm particulates should be worn by all staff and visitors entering the room to prevent inhalation of aerosolized mycobacteria. The room door should remain closed; patients leaving their room should wear a mask. Patients with smears positive for acid-fast bacilli should remain on respiratory precautions until they have received adequate therapy for at least two weeks, show clinical improvement, and show a decrease in acid-fast bacilli on quantitative sputum smears.

Screening and secondary prophylaxis are crucial in the care of persons with HIV. The rate at which active tuberculosis develops in HIV-infected persons with positive skin tests is 10% per year in the absence of prophylaxis, compared with a 10% total lifetime risk in HIV-negative adults who have positive purified protein-derivative (PPD) skin tests. The prevalence of anergy increases with the progression of HIV infection: only 10% of HIV-positive patients with T-helper ($CD4^+$) cell counts of 200 to 400 cells $\times 10^6$ per liter (200 to 400 per mm^3) are anergic, compared with two thirds of those with $CD4^+$ counts of less than 200 $\times 10^6$ per liter. Purified protein-derivative skin testing with two controls should be done as early as possible in patients at risk for HIV infection and, if negative, should be repeated every 6 to 12 months until anergy supervenes.

Because of the likelihood of a reduced cutaneous immune response and the serious consequences of a false-negative result, a positive PPD test is defined as 5 mm or more of induration, in contrast to the 10-mm cutoff used in non-HIV-infected people. Anergy is defined as 2 mm of induration or less in response to all three antigens. Persons with positive PPD tests are treated for one year with a regimen of isoniazid, in contrast to the six-month regimen used in HIV-negative patients. Studies are under way to assess the effectiveness of shorter courses. Chemoprophylaxis results in a severalfold reduction in the incidence of progression to active disease and is administered to HIV-positive patients regardless of age or length of time since PPD conversion. Chemoprophylaxis of anergic patients with HIV is also recommended when a patient is at high risk for TB by social factors, has a history of untreated positive PPD tests at any time in the past, or has been in close contact with an infectious patient with TB. Patients infected with HIV who are exposed to multidrug-resistant TB should receive prophylaxis with at least two drugs to which the presumed source strain is shown to be susceptible. In these patients, the Centers for Disease Control and Prevention recommends a regimen that includes pyrazinamide and ethambutol hydrochloride or pyrazinamide and a fluoroquinolone (ciprofloxacin or ofloxacin).

Human immunodeficiency virus-infected patients with active tuberculosis that is not drug-resistant generally respond well to therapy. Because of the increasing prevalence of multidrug-resistant TB, initial therapy with four drugs—isoniazid, 300 mg; rifampin, 600 mg; pyrazinamide, 25 mg per kg; and ethambutol, 15 mg per kg—is recommended for all patients, immunocompromised or not. Appropriate modifications are then made as sensitivities become available from sputum cultures. If exposure to a multidrug-resistant strain is suspected, if the patient has been previously treated for TB, or if positive sputum cultures persist after three months of compliance with treatment, a specialist should be consulted. In general, a regimen for multidrug-resistant TB should contain at least three drugs to which the organism is susceptible and may involve 18 months or more of treatment.

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Hormonal Therapy for Metastatic Prostate Cancer

THE MEDIAN TIME from the diagnosis of metastatic prostate cancer to death is 2.5 years. The vast majority of the 34,000 deaths per year from prostate cancer in the

United States will be due to the progression of metastatic prostate cancer. Since 1941 androgen deprivation has been the standard of care for the treatment of patients with metastatic prostate cancer. The equivalence of orchiectomy, estrogen (diethylstilbestrol) administration, and luteinizing hormone-releasing hormone (LH-RH) analogues such as leuprolide acetate (Lupron Depot, TAP Pharmaceuticals) and goserelin (Zoladex, ICI Americas), which reduce testicular androgen production to castrate levels by pituitary desensitization, has been demonstrated. All of these treatment modalities result in a loss of potency and libido. Whereas estrogen use avoids the development of hot flashes and gynecomastia sometimes seen with orchiectomy and LH-RH analogue administration, and certainly is less expensive, its association with substantial thromboembolic toxicity and mortality, even when used in attenuated doses, makes it less desirable.

More recently the contribution of the adrenal glands to the total androgen pool has become apparent: 5% to 10% of circulating testosterone levels and 25% to 40% of intraprostatic dihydrotestosterone content are of adrenal origin. The importance of this alternate androgen pathway has been confirmed by the clinical observation that suppressing or blocking adrenal androgen function results in a 15% to 30% response rate in patients with metastatic prostate cancer who have relapsed after castration.

Several methods of interfering with adrenal androgen expression are in use. Ketoconazole and aminoglutethimide inhibit steroidal ring synthesis, thereby suppressing all steroid production, including testosterone of testicular and adrenal origin. In addition to the need for hydrocortisone replacement, the nausea sometimes experienced with these drugs has limited their use, primarily relegating them to the "salvage" setting. Antiandrogens are compounds that bind to the androgen receptor found in prostate cancer cells. The steroidal antiandrogens, cyproterone acetate and megestrol acetate (Megace, Bristol-Myers), also exhibit progestational activity, suppressing the hypothalamic-pituitary-gonadal axis and thereby causing impotence and loss of libido. Furthermore, both megestrol and cyproterone acetate have associated thromboembolic side effects. By contrast, the nonsteroidal antiandrogens (flutamide, nilutamide, and casodex) lack progestational or thrombogenic side effects. Only megestrol and flutamide (Eulexin, Schering) are approved for use in the United States at this time.

The attractiveness of using antiandrogens as primary monotherapy for metastatic prostate cancer lies in their ease of use and potential to avoid impotence and loss of libido. Two monotherapy trials using two different antiandrogens, however, have shown this approach to be inferior to conventional testicular androgen ablation.

An understanding of the adrenal contribution to the total testosterone pool has prompted several randomized trials comparing the use of combined androgen blockade (the addition of an antiandrogen to the interruption of testicular androgen production) with that of testicular androgen deprivation alone. The largest series to date is the National Cancer Institute (USA) intergroup study that was initiated in 1985. This was a double-blind, placebo-controlled trial in which 603 patients with stage D2 prostate carcinoma were randomly allocated to receive leuprolide acetate plus placebo versus leuprolide acetate plus flutamide. The time to disease progression (16.5 months versus 13.9 months) and overall survival (35.6 months versus 28.3 months) were superior with combination therapy. Of interest, the superiority of using combined therapy over leuprolide alone was most apparent in patients who had been prospectively stratified into a good performance and minimal disease category. These patients had more than a 20-month survival advantage when treated with combined therapy. It should be noted that this trial allowed patients with progressive disease who had been on the placebo arm to "cross over" to the other arm by adding flutamide to their regimen. Thus, this trial showed that immediate combined androgen blockade is preferable to the delayed addition of an antiandrogen after the disease progresses.

Four other large randomized trials have compared combined androgen blockade with various forms of gonadal androgen deprivation (monotherapy). All but one have found an advantage in overall survival for combined androgen blockade (six to seven months). Although the body of evidence in favor of combined androgen blockade is growing, enthusiasm for this approach must be tempered by its expense—the addition of flutamide costs between $200 and $300 extra each month—and by the fact that a few trials have reported no advantage.

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Current Diagnosis and Treatment of *Helicobacter pylori*

THE ROLE OF *Helicobacter pylori* in the pathogenesis of peptic ulcer disease and chronic antral gastritis is being increasingly recognized. Although its relationship to functional dyspepsia and gastric adenocarcinoma is still uncertain, several studies have shown that relapse or remission of duodenal ulcer is strongly associated with the presence or absence of *H pylori* colonization of the gastric mucosa. The incidence of recurrence of duodenal ulcer during the first year after healing is substantially less for patients in whom *H pylori* is eradicated. Preliminary data suggest a similar role of *H pylori* in patients with gastric ulcer disease.

Although the mechanisms of ulcer formation by *H pylori* remain obscure, the strong evidence implicating the organism as a major factor in ulcerogenesis has modified our approach to the evaluation and management of patients with gastroduodenal ulcers. Patients with compli-

cated ulcer disease—bleeding, recurrence, intractability, perforation—are most often considered for anti-*H pylori* therapy. Some controversy exists, however, regarding whether to treat every patient with uncomplicated *H pylori*-associated gastric or duodenal ulcer on first presentation. Most experts recommend confirming the presence of *H pylori* infection before initiating therapy. Gastric antral biopsy for histologic examination—with special stains such as Warthin-Starry or modified Giemsa—is the most sensitive method of detecting infection. Because *H pylori* produces large amounts of urease, rapid urease tests (CLOtest) are widely used to detect the organism in biopsy specimens. Cultures for *H pylori* are primarily used to determine sensitivity to antimicrobials in resistant strains.

Urea carbon breath tests (carbon 13 or carbon 14 tracer) are noninvasive methods that can be used for monitoring short-term response to therapy, whereas changes in serologic titers may require several months and therefore are less useful for this purpose. Urea breath tests are not widely available for clinical use at this time.

The most widely used regimen for *H pylori* consists of triple therapy with tetracycline (500 mg four times a day), bismuth subsalicylate (two tablets four times a day with meals and at bedtime), and metronidazole (250 mg three times a day with meals), each taken for 14 days. Amoxicillin (500 mg four times a day) is an alternative to tetracycline. The eradication of *H pylori* is confirmed by endoscopic biopsy or a urea breath test one month after completion of therapy. Although with triple therapy successful eradication has been reported in as many as 90% of patients, it is associated with problems of compliance. Substantial side effects have been reported in as many as 30% of patients, including headache, dizziness, nausea, diarrhea, antibiotic-associated colitis, drug hypersensitivity, sore mouth and tongue, and paresthesia. Furthermore, treatment failures have been associated with resistance to metronidazole. Metronidazole-resistant strains may respond to retreatment with triple therapy that substitutes clarithromycin for metronidazole, or quadruple therapy by adding erythromycin. More recently, combination therapy with omeprazole (20 mg twice a day) and amoxicillin (500 mg three times a day) for a minimum of two weeks has resulted in an eradication rate of more than 80% and appeared to be better tolerated than the standard triple therapy. Ongoing studies should reveal the pathogenetic mechanisms of ulcer formation by *H pylori* and determine the optimal regimen for its eradication.

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Heparin Therapy for Venous Thromboembolism

THE EFFICACY OF HEPARIN THERAPY for pulmonary embolism and deep venous thrombosis is well established, and heparin therapy has been the standard of care for decades. The monitoring of heparin therapy has evolved from the use of whole-blood clotting times to that of the activated partial thromboplastin time (aPTT). The recommended lower limit of the therapeutic range of aPTT is 1.5 times the control aPTT. Despite this experience with heparin, recent reviews of heparin therapy have shown that heparin is frequently underdosed. There appear to be two main reasons for this.

Patients with venous thromboembolism have a variable response to heparin, frequently requiring higher doses to achieve a therapeutic level. Heparin is eliminated more rapidly in patients with pulmonary emboli. Furthermore, higher doses of heparin are required to prevent the extension of existing venous thrombosis than to prevent its formation.

The major reason for an underdose of heparin is concern about the risk of bleeding. An association between the incidence of bleeding and the dose of heparin or the aPTT level has been postulated, but a recent study suggests that other risk factors are more important than the initial dose of heparin. Of note, there was no association of bleeding with supratherapeutic aPTT levels in this study.

If there were no therapeutic consequences of heparin underdosage, then our usual heparin therapy would not need to be changed. Unfortunately, failure to exceed the lower limit of the therapeutic range (aPTT 1.5 times the control aPTT) results in a markedly increased risk of recurrent venous thromboembolism.

How then can subtherapeutic heparin therapy be avoided? Expert consensus is that physicians should continue to give 5,000 to 10,000 units of heparin in an intravenous bolus but that the initial intravenous infusion should be at least 1,300 units per hour. The first aPTT should be measured six hours after starting therapy and adjustments made according to a recommended protocol rather than clinical intuition. One protocol is based on the Dade-Actin FS reagent, which has a normal aPTT range of 27 to 35 seconds. An aPTT between 55 and 85 seconds is therapeutic, and no adjustments are necessary. For an aPTT between 46 and 54 seconds, the infusion should be increased by about 125 units per hour. For an aPTT of less than 45 seconds, another bolus of 5,000 units of heparin should be given and the infusion increased by about 250 units per hour. For an aPTT between 86 and 110 seconds, the infusion should be held for an hour and decreased by about 125 units per hour. For an aPTT greater than 110 seconds, the infusion should be held for an hour and then decreased by about 250 units per hour. Whenever there is a change in the infusion, an aPTT should be checked in four to six hours or once a day if the aPTT is in the therapeutic range. When this protocol was used, 2% of patients had subtherapeutic aPTT levels at 24 hours compared

with 60% from a review of heparin therapy not using the increased initial heparin dosage nor the protocol to adjust the heparin infusion.

A further complicating factor is that aPTT reagents are not standardized. Each institution's aPTT therapeutic range should be calculated to correspond to heparin levels of 0.2 to 0.4 units per ml by protamine titration. This may result in a different therapeutic range, depending on the type of reagent, and may necessitate modifying the heparin protocol. In the near future, heparin monitoring should be standardized, much as the international normalized ratio has standardized warfarin monitoring.

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Alerts, Notices, and Case Reports

Acute Histoplasmosis Acquired in Mexico

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Histoplasma capsulatum is a fungus that is endemic in the Ohio and Mississippi river valleys of the central United States.[1,2] Patients from these areas with suggestive clinical signs and symptoms are usually evaluated for possible histoplasmosis. Many American physicians are unaware that *H capsulatum* is endemic in 31 of the continental 48 United States[1,3] and in many other parts of the world.[3,4] Most comprehensive American epidemiologic reviews fail to emphasize that Mexico is an endemic area. We report a case of severe acute histoplasma pneumonia and fungemia in a patient who contracted the disease during a visit to Mexico.

Report of a Case

The patient, a 30-year-old man, was seen in the emergency department because of severe dyspnea. He had been in good health until three weeks before admission, when bifrontal headache, cough productive of green sputum, dyspnea, and fever to 38.9°C (102°F) developed while he was in Mexico. He used acetaminophen without relief and subsequently went to a physician who noted right lung crackles. The patient was given cefuroxime for eight days, but obtained no relief. He had no history of exposure to animals or to sick people. He was a nonsmoker, never used illicit drugs, and had no blood transfusions, homosexual contacts, or contact with prostitutes. He was a day laborer in the domestic construction trade and had immigrated to this country from Mexico in 1985. He had been in Mexico City and the states of Hidalgo and Colima for three months but returned home to San Jose, California, 1½ weeks before admission. On his return home, the patient drove from Mexico City and entered the United States through Nogales, Arizona.

The patient was diaphoretic, in moderate distress due to dyspnea, and was unable to talk in full sentences. He was coughing up copious amounts of blood-tinged purulent sputum. His blood pressure was 110/67 mm of mercury, his pulse rate was 110 beats per minute, the respiratory rate was 28 breaths per minute, and his temperature initially was 37.2°C and increased to 40°C on the first hospital day. The head and neck were unremarkable except for herpes labialis. There was no peripheral lymphadenopathy, the skin was normal, and the results of a cardiovascular examination were unremarkable. There were diffuse inspiratory crackles over all lung fields without wheezes. The abdomen and extremities were normal, and he had no hepatosplenomegaly.

A chest roentgenogram showed a diffuse interstitial nodular infiltrate in a peribronchial distribution bilaterally without adenopathy, pleural fluid, or cardiomegaly (Figure 1). His leukocyte count was 8.0×10^9 cells per liter (8,000 cells per mm^3) with 0.80 (80%) neutrophils, 0.07 (7%) band forms, 0.11 (11%) lymphocytes, and 0.02 (2%) monocytes; the hematocrit was 0.42 (42%). A specimen of radial arterial blood taken with the patient breathing room air showed a pH of 7.50, a P_{CO_2} of 31 mm of mercury, and a P_{O_2} of 42 mm of mercury. A computed tomographic scan of the head done without a contrast medium was normal, and a lumbar puncture revealed no leukocytes, 6 erythrocytes $\times 10^6$ per liter (6 per mm^3), a total protein level of 0.15 grams per liter (15 mg per dl), and a glucose level of 3.0 mmol per liter (54 mg per dl).

It was initially thought that the patient had a pneumonia most suggestive of infection with *Coccidioides immitis*, but tuberculosis was strongly considered. A regimen of broad-spectrum antibiotics was started consisting of intravenous erythromycin, amphotericin B, and methylprednisolone sodium succinate and oral isoniazid, rifampin, pyrazinamide, and ethambutol hydrochloride. Supplemental oxygen was administered with a 100% nonrebreather face mask plus nasal cannula at 6 liters per minute. The patient improved remarkably by the second hospital day and required only nasal oxygen at 2 liters per minute on the third day. Oral ketoconazole was substituted for intravenous amphotericin B on the sixth hospital day, and the patient was discharged on the ninth day.

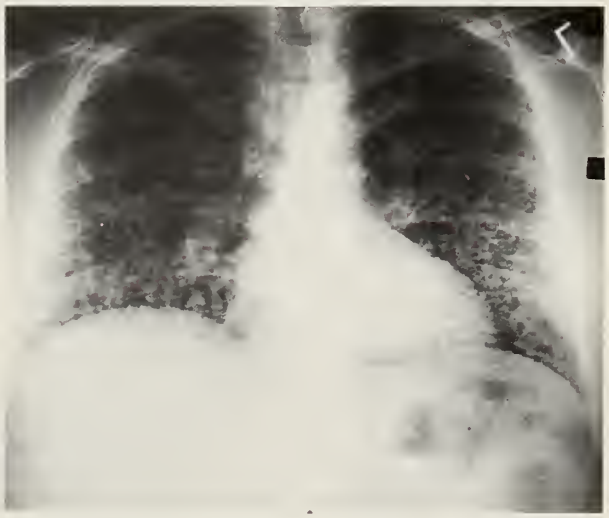

Figure 1.—The chest film shows interstitial nodular infiltrates of both lung fields.

(Kirsch CM, Jensen WA, Kagawa FT, Campagna AC: Acute histoplasmosis acquired in Mexico. West J Med 1994; 160:257-259)

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Serologic tests were negative for the human immunodeficiency virus type 1 and *C immitis* antibodies, and *Cryptococcus neoformans* antigen was not detected in the blood. All sputum specimens were negative for fungal organisms (using potassium hydroxide) and acid-fast bacteria. A fungus was identified in cultures of one blood and two sputum specimens on the 12th day, which subsequently proved to be *H capsulatum*. All cultures for acid-fast organisms have remained sterile. A second chest film done six weeks after admission showed pronounced resolution of the noncalcified infiltrates.

The patient has been treated with oral ketoconazole, 400 mg a day, for more than three months without problems. He continues to feel well, has gained 7.25 kg (16 lb), and has returned to work. The patient has consistently denied any exposure to bats, birds, or bird guano, spelunking, or travel to areas in the United States known to be endemic for *H capsulatum*.

Discussion

Histoplasma capsulatum is a dimorphic fungus that inhabits temperate areas worldwide and is endemic in the Americas.[1,3,4] Its geographic distribution in the Americas is best documented in the Mississippi and Ohio river valleys of the central United States[1,5] and Central and South America.[2-5] Human infection with *H capsulatum* is caused by inhaling infectious spores released from fungus growing in soil.[1,3] Bird and bat guano seem to facilitate the formation and growth of *H capsulatum* spores.[1,3] The clinical presentation of histoplasmosis may be similar to that of tuberculosis,[4] but *H capsulatum* is not known to be transmissible from one infected person to another.[1,3,5] Therefore, as noted in 1956, "the factor of primary significance in histoplasmosis is geography: where a man lives, rather than with whom he lives, is of major importance in determining his chances of becoming infected with the fungus."[4(p247)] The occurrence of histoplasmosis in nonendemic areas is thought to be due to the acquisition of disease in patients who have migrated from endemic areas after acquiring a primary infection,[6] possibly due to a reactivation of previous infection in patients from endemic areas who have decreased immune function[7] or to primary infection acquired from contact with "microfoci" or "point sources" outside the endemic area.[2] Microfoci are locations in endemic or nonendemic areas such as caves, buildings, bird roosts, chicken coops, and trees that are contaminated with bird or bat excrement.[1] Some patients with acute histoplasmosis cannot recall such exposures. Our patient had severe acute histoplasma pneumonia and fungemia,[8] and his chest film suggests a massive acute inhalational exposure.[1] The incubation period is probably 3 to 30 days with a mode of 14 days[1,9] and may be even shorter in patients with a massive spore inhalation or previous histoplasma fungal infection.[1] Our patient resided in Mexico for more than two months before becoming symptomatic and probably acquired his infection there.

Since the original description of histoplasmosis by Samuel Darling in Panama in 1906,[10] most epidemiologic reviews indicate that the disease is well described in Central and South America, but only a few reviews even superficially include Mexico.[2-4] The prevalence of *H capsulatum* and the incidence of histoplasmosis in Mexico are not well documented in the English-language medical literature and consequently are not widely appreciated by American physicians. Many epidemics of histoplasmosis have been described in Mexico since the first case description in 1943,[11] and these epidemics have not been isolated to any particular geographic area of the country.[12,13] In fact, histoplasmosis has been described in 13 of 32 Mexican states as of 1963[12] and 15 states as of 1964,[14] and its geographic distribution is not limited by climate or latitude.[12,14] Most of these outbreaks (96% of cases) seem to have been associated with bat-dung contact occasioned by harvesting for fertilizer or cleaning during restoration.[12,14] There were 12 epidemics and 6 isolated cases of histoplasmosis involving 292 patients described from 1959 to 1964.[14] One of the best documented of these epidemics occurred in 1960 among 65 workers who were hired to clean a 60-year-old mile-long tunnel in the state of Colima.[15] Histoplasmosis occurred only in the 50 of 59 workers who actually worked inside the tunnel. The incubation period was seven to ten days, 6 of the 50 patients had severe pneumonia, and 3 of the 6 patients died. The massive inhalational exposure produced a diffuse micronodular pattern on chest film in most patients, and *H capsulatum* grew in the blood cultures of 2 of the patients who died. Our patient visited the state of Colima during his return to Mexico, where he did some domestic renovation and home construction. His illness was similar to that of the most severely infected Colima workers. The French Canadian medical literature contains a similar report of three Canadians who visited Mexico and contracted histoplasmosis while exploring caves there.[16] Our patient, as well as the French Canadians, had a clinical presentation similar to that of tuberculosis. The Mexican medical literature indicates that histoplasmosis and tuberculosis have similar clinical presentations[11] and that evaluations that fail to find tuberculosis in such patients should prompt an investigation for histoplasmosis.[17]

We conclude that *H capsulatum* and histoplasmosis exist in Mexico and are well documented in the Mexican medical literature and in French Canadian case reports. American physicians do not commonly read Mexican or French Canadian reports and consequently are not aware of its prevalance there. Patients who have visited Mexico and who appear to have an illness suggestive of a fungal pneumonia should be evaluated for possible histoplasmosis.

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Factitious Simulation of Systemic Lupus Erythematosus

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SELF-INFLICTED INJURIES AND DISEASES have been recognized since Biblical times. In the Middle Ages, hysterics were known to place leeches in their mouths to simulate hemoptysis and to abrade their skin to reproduce skin conditions.[1] Gavin in 1843 distinguished between malingering—feigning illness for financial compensation—and simulating illness for inexplicable motives.[2] In 1951 Asher identified the latter syndrome, naming it after the 18th century German nobleman with a predilection towards embellishment: Baron Karl Friederich Hieronymus von Münchausen.[3]

Munchausen syndrome is a variant of chronic factitious illness in which a patient's plausible presentation (often emergent and dramatic) of factitious symptoms and disease is associated with many hospital admissions.[4] Although this condition is thought to be rare, its presentation is not uncommon as persons with the syndrome drift from hospital to hospital, often with more than one admission at each. Invasive diagnostic studies and surgical procedures are common in these patients. Since the original description of this syndrome, many reports have documented the spectrum of disorders that have been simulated. We have not, however, seen any reports of a man with simulated systemic lupus erythematosus.

(Apfelbaum JD, Williams HJ: Factitious simulation of systemic lupus erythematosus. West J Med 1994; 160:259-261)

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Report of a Case

The patient, a 29-year-old man with a history of systemic lupus erythematosus (SLE), was seen at the emergency department of the University of Utah Medical Center (Salt Lake City) because for eight days he had had right flank pain radiating to his right groin, nausea, vomiting, and gross hematuria. He had been seen at another facility where he was diagnosed with a kidney stone and treated with narcotics and intravenous hydration. Although he said he was "violently" allergic to intravenous contrast dye, the patient brought with him an intravenous pyelogram. He was seen in the urology clinic where his pyelogram was interpreted as normal without any signs of renal stones. He was then admitted for the evaluation of possible lupus nephritis.

The patient said he had been diagnosed with lupus five years ago at an unrecalled hospital. He said his symptoms at that time were "bursitic arthralgias," myalgias, low leukocyte count, photosensitivity (described as a rash on his arms and legs after sun exposure longer than 20 minutes), photophobia, pleuritic chest pain, a positive antinuclear antibody test, and a malar rash. In addition, the patient described "blackouts," which he presumed to be some type of seizure, that occurred from once a week to once a month, were preceded by a feeling of dizziness, lasted for several seconds, and were followed by disorientation for several hours. He never lost consciousness and did not have any incontinence during these episodes; none of them had ever been witnessed. He said he had a previous electroencephalogram at an unknown facility with unknown results. The patient also gave a history of a positive human immunodeficiency virus (HIV) test five years before, previous hepatitis, and previous nephrolithiasis.

On examination, the patient's vital signs were stable and he was afebrile. He appeared to be resting comfortably and conversed easily, often requesting medication to relieve the pain in his back. Any palpation of the patient was met with groans and exclamations of distress. His discomfort seemed to be greatest at the right costovertebral angle with considerable tenderness throughout his back and extremities. He had no lymphadenopathy or rashes. His cardiovascular system was normal, and his lungs were clear to auscultation. The chest pain was reproducible with sternal pressure. His abdomen was tender to palpation in the right upper and lower quadrants. The results of his neurologic examination were within normal limits without any focal signs, and extremities were remarkable only for several areas of hypopigmentation on his upper extremities and multiple punctate lesions on the pad of his left index finger.

Laboratory data showed a leukocyte count elevated at 10.7 cells $\times 10^9$ per liter (10,700 cells per mm^3) with a normal differential cell count, a hematocrit of 0.41 (41%), a platelet count of 211 $\times 10^9$ per liter (211,000 per mm^3), normal electrolytes, normal liver function test results, and a sedimentation rate of 2 mm per hour. On analysis the urine was "cloudy" with a specific gravity of 1.020, a pH of 7.0, without protein, nitrate, or ketones, and without leukocytes or casts. There were 10 to 20 erythrocytes vis-

ABBREVIATIONS USED IN TEXT

HIV = human immunodeficiency virus
SLE = systemic lupus erythematosus

ible per high-power field; they were not crenated. The antinuclear antibody test was negative, and serum levels of complement components C3 and C4 were normal. The rapid plasma reagin test was nonreactive, and a test for the hepatitis B core antibody was positive. His chest film showed low lung volumes, linear atelectasis, poor inspiratory effort, and a heart size at the upper limits of normal.

The patient was admitted late in the afternoon and given meperidine hydrochloride, 25 mg intravenously every four to six hours for pain, with subsequent full workup done the following day. During this evaluation he said that he had never had a malar rash and had a second HIV test a month before that was negative. He said that he had been admitted to a hospital in San Francisco, California, in Colorado, and in various places in Utah but could not provide the names of any of these hospitals. In addition, he gave the name of a local physician as his primary care physician but said that she would no longer see him as he could not afford to pay his bills. The nephrology service was consulted and recommended a kidney biopsy, providing the rest of his workup was consistent with SLE. Later that day the patient's former physician was contacted and reported that the patient had an extensive history of presenting to emergency departments with flank pain, hematuria, and an alleged allergy to intravenous contrast dye, frequently obtaining narcotic analgesia, and occasionally being admitted to the hospital. She thought that his hematuria was factitious from self-inflicted puncture wounds. In addition, he was HIV negative by a test done in her office within the previous three months. She had terminated their physician-patient relationship because she specializes in the treatment of HIV-positive patients and she felt he had a psychiatric illness that she was not qualified to treat. He had refused her many referrals for psychiatric evaluation and treatment.

This information was discussed with the patient, who vehemently denied any past psychiatric referrals or previous episodes of hematuria. When asked how he received the pinpricks to his left index finger, he said that he got them from "painting." The patient was asked if he would produce an observed urine specimen to test for blood, which he declined to do. He was offered referral to the psychiatric service but elected to be discharged with outpatient follow-up with the psychiatric and rheumatology services. He did not keep either appointment.

Comments

The classic features of the Munchausen syndrome are as follows: a socially isolated young adult, pathologic lying, numerous appearances at many hospitals, dramatically feigned severe illness of an acute and harrowing nature, factitious evidence of disease, a medically informed or convincing background history, history of several surgical procedures, evasiveness in manner, frequently a tendency to drug addiction, indignant departures from hospitals against medical advice when discovery has occurred or seems imminent, a failure to report for follow-up appointments, and the absence of any readily discernible ulterior motive.[1,3,5-7] The full spectrum of features may not appear until late in the course of this syndrome.[6]

A great many disorders have been mimicked, limited only by the creativity of the patient. Cases of feigned Goodpasture's syndrome[1]; small bowel obstruction, hematemesis, and peptic ulcer disease[3]; sickle cell anemia and crisis[5]; seizures or neurologic manifestations[8]; renal lithiasis[9,10]; asthma, fever, and Bartter's syndrome[11,12]; systemic lupus erythematosus[11,13]; abdominal pain, emesis, cardiac complaints, and dermal conditions[8]; migraine headaches, chronic dislocating shoulder, tic douloureux, and abscessed teeth[10]; and diarrhea, urinary tract infection, meningitis, hyposthenuria, hyperthyroidism and hypothyroidism, and extremity lymphedema[12] have all been reported.

In systemic lupus erythematosus, 11 criteria have been designated for classification, with the presence of 4 criteria, either serially or simultaneously, required for diagnosis.[14] Our patient had, by history, 8 of the 11 criteria. His complaints of photosensitivity did not involve all sun-exposed areas. His claimed malar rash and arthritis were unsubstantiated by physical examination. His complaint of pleuritic chest pain was convincing, but he had no pericardial friction rub, pleural effusion, or other objective evidence of serositis. His renal symptoms, without proteinuria or casts and with noncrenated erythrocytes, are almost certainly a factitious addition of blood to his urine specimens. The patient was neurologically intact, and his history is inconsistent for the generalized tonic-clonic seizures classically seen in SLE. The patient had neither anemia, leukopenia, lymphopenia, nor thrombocytopenia. He was nonreactive for rapid plasma reagin, and his antinuclear antibody test was negative. His method of falsifying hematuria by adding blood from self-inflicted needle sticks is not unique.[4,5,8,10-13,15] It is of interest that the patient is right-handed. As Shafer and Shafer noted: "Factitious lesions are rarely seen on the right hand or wrist of a right-handed person or on the left hand or wrist of a left-handed person."[12(p597)] Therefore, it would be prudent for a physician suspecting Munchausen or any other factitious syndrome to search the nondominant extremity for possible signs of injury.

We initially suspected this patient of being addicted to narcotics. Although narcotic use (especially meperidine) and addiction can be a facet in Munchausen's,[1,3-10,12,13,15-17] these patients do not have withdrawal symptoms on stopping the drug, nor is obtaining drugs the goal of their admission to hospital.[6,8,10] If our patient's goal was to obtain narcotics, he could have avoided an intravenous pyelogram and continued his excursions to various emergency departments, receiving narcotics for the outpatient treatment of a presumptive kidney stone.

The appropriate treatment is intensive psychiatric therapy. Unfortunately, patients with the Munchausen syndrome are resistant, with few recorded "cures."[17] The best

treatment is early recognition. Antipathy at being deceived by these patients is understandable. Beguiled physicians should realize, however, that although this disorder is "voluntary" in the sense that patients know they are pretending, they are unable to stop. Rather, they deceive themselves with their own fabrication. Moreover, physicians need to be the patients' advocates in deciding on appropriate therapy. Only in this way can unnecessary operations and invasive diagnostic studies, with their inherent risks of complications, be avoided and the correct treatment be attempted. In addition to the risk of iatrogenic injury, the time and expense saved by rapid recognition, especially in view of limited health resources, may be the greatest benefit.

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Black Widow Spider (*Latrodectus mactans*) Bite During Pregnancy

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SPIDERS OF THE GENUS *Latrodectus* are found in all parts of the United States and throughout the world. They are common in the southwestern states and are found in and around domestic areas. Bites are not uncommon despite the docile nature of spiders—they seem to bite only when provoked. Information about spider bites and envenomation during pregnancy is lacking, but pregnancy does not protect a woman from this type of accident.[1,2] We present a case of latrodectism occurring in a pregnant woman and discuss the literature of black widow spider bites during pregnancy.

(Handel CC, Izquierdo LA, Curet LB: Black widow spider [*Latrodectus mactans*] bite during pregnancy. West J Med 1994; 160:261-262)

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Report of a Case

The patient, a 36-year-old woman at 22 weeks' gestation, was admitted to the University of New Mexico Hospital/Bernalillo County Medical Center (Albuquerque) because of restlessness, pain and cramping in her legs, hips, and lower back, shortness of breath, and chest tightness. She had been bitten on her upper left thigh while in bed. The patient found a spider in the bedsheets that she killed and brought with her to the hospital. It was identified as a "black widow" spider. The patient did not have uterine cramping, vaginal bleeding, or rupture of membranes.

On physical examination the patient had a temperature of 37.3°C, a blood pressure of 156/81 mm of mercury, a pulse rate of 92 beats per minute, and a respiratory rate of 16 per minute. She was alert and oriented but appeared anxious. The examination elicited no abnormalities except that her upper left thigh had about a 2-mm erythematous papule on the lateral aspect. The deep tendon reflexes were normal. Her cervix was closed, long, and high, and no vaginal bleeding was noted. Ultrasonography revealed a single live fetus, the size of which was consistent with dates. Laboratory studies revealed a leukocyte count of 10.9×10^9 per liter (10,890 per mm^3) with 0.82 (82%) neutrophils.

The patient was initially given 10 ml of a 10% solution of calcium gluconate, 5 mg of diazepam, and 5 mg of morphine sulfate. She experienced some relief, but the muscle cramping and pain soon returned. She was given another 10-ml dose of a 10% solution of calcium gluconate and 5 mg of morphine sulfate. A skin test was done of the antivenin, and a standard dose—one 2.5-ml vial of antivenin in 50 ml of normal saline solution—was administered intravenously over 15 minutes. Within an hour of the administration of the antivenin, the patient indicated that she did not have any muscle cramping or pain, and she no longer appeared anxious. She was discharged the following day in good condition.

Discussion

The genus *Latrodectus* comprises several species. *Latrodectus mactans* (black widow), *Latrodectus geometricus* (brown widow), *Latrodectus bishopi* (red-legged widow), *Latrodectus variolus*, and *Latrodectus hesperus* are the species found in North America. Although they differ in their markings and color, their potent neurotoxins are similar and respond to the same antivenin. Generally speaking, only the female spider is considered a threat to humans. The male's small size and small che-

licerae or fangs are incapable of delivering dangerous envenomation.[1]

The venom is oily and comprises several different components. The α-latrotoxin (molecular weight 130,000), the potent neurotoxin responsible for the symptoms associated with envenomation, binds to the lipid membrane of neurons and causes a synaptic release of a neurotransmitter.[2] This results in a dramatic release of acetylcholine at the neuromuscular junction, causing muscle contraction.

The most common symptoms are muscle pain, muscle spasms, and abdominal rigidity. Other symptoms include perspiration (localized or generalized), nausea, vomiting, diarrhea, cutaneous hyperesthesias, headache, tachycardia, bradycardia, arrhythmias, hypertension, convulsions, priapism, and shock. The symptoms generally occur within 30 minutes to an hour of the bite and usually resolve spontaneously over 12 to 48 hours. General body aches, weakness, fatigue, paresthesias, and perspiration rarely persist for weeks or months. Death is rarely the result of latrodectism. After moderate envenomation, subsequent bites may produce an increased local effect and little or no systemic effects.[1,2]

There are no serologic tests to confirm the diagnosis of latrodectism. If the patient brings in the spider, the diagnosis is not problematic. The site of the bite may or may not have a discernible mark, and symptoms are nonspecific. There are cases of patients who have undergone surgical exploration for "acute abdominal pain" or who were admitted to psychiatric wards.[1,2] Thus, a history of a bite or possible exposure becomes crucial to the proper diagnosis and treatment.

Standard treatment can be found in most textbooks of emergency medicine. After initial wound care, most sources recommend the use of calcium gluconate, muscle relaxants, and narcotic analgesics for mild cases. Tetanus toxoid should be considered in all cases. There is disagreement regarding the use of the antivenin. Some clinicians advocate administering antivenin only in severe cases of envenomation and not in patients with moderate envenomation because of the risk of serum sickness. Others point out that the amount of antivenin for black widow bites is small compared with the amount necessary for snake bites, and that even if serum sickness were to occur, it would most probably be mild.[1,2]

Clearly not much is known about black widow bites during pregnancy. There are few reports or studies about the effects of envenomation during pregnancy. We can, however, draw some conclusions with the information we have.

α-Latrotoxin is a fairly large compound and unlikely to diffuse across the placenta. It is unlikely to have direct effects on the fetus, but without good evidence we cannot be sure.

Some of the possible effects of envenomation are accepted as being deleterious to the fetus. For example, certain cardiac arrhythmias can compromise maternal and fetal oxygenation. Hypertension, shock, and convulsions are also known to be potentially harmful to the fetus. Although abdominal cramping may be severe in some cases, it is not clear that such cramping could be responsible for a spontaneous abortion or preterm labor. Only when a substantial number of cases or studies have been reported will we fully understand all the ramifications of envenomation during pregnancy.

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Special Series

A Brief History of Health Care Quality Assessment and Improvement in the United States

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We review the history and current efforts to assess and improve health care in the United States. This process has involved a host of government agencies and commissions, professional organizations, insurance underwriters, corporations, and more recently, market forces. Traditional approaches to quality control have stressed case-by-case analysis and identifying outliers. Newer approaches include creating practice guidelines and profiles of hospitals and physicians. The joint goals of quality improvement and cost control can best be realized if institutions and practitioners embrace these new approaches and use them to enhance their performances.

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Defining the quality of health care requires knowing how much people benefit from health services, as measured by factors like the results of specific diagnostic and therapeutic procedures, patient satisfaction, and society's sense of well-being. Because it is difficult to maintain quality while decreasing costs, each is receiving equal attention in current debates on reform, particularly in the context of managed care and integrated health systems. As reform proceeds, one of the greatest challenges will be to contain costs and simultaneously improve quality without imposing external controls.

We outline the history and current state of health care quality assessment and improvement in the United States. We also review professional and governmental programs that regulate quality and assure physicians' qualifications, malpractice lawsuits and the demands of insurance companies, and changes in the organization and provision of health care services. We stress hospital and medical staff activities because regulatory agencies have in the past focused on them; other important arenas such as nursing homes are not discussed.

Voluntary Professional Programs

Organized Medicine

In the early 19th century, American medicine was disorganized and of poor quality, with the control of medical education in the hands of proprietary and for-profit institutions. Several organizations and individuals undertook to correct this. Founded in part for this reason in 1847 as a confederation of state and local societies, the American Medical Association (AMA) encouraged Abraham Flexner in research that by 1910 led to his *Report to the Carnegie Foundation,* which documented the deplorable state of the nation's medical schools and major hospitals.[1,2] In the same year Ernest Codman of Boston's Massachusetts General Hospital noted the need to improve hospital conditions and to track patients to verify that their care had been effective. Although few followed Codman's lead, his efforts contributed to the American College of Surgeons' establishing its Hospital Standardization Program in 1917.[3]

The first five standards focused almost entirely on care within hospitals. Known as the "minimum standards," they called for the following:

- Organizing hospital medical staffs;
- Limiting staff membership to well-educated, competent, and licensed physicians and surgeons;
- Framing rules and regulations to ensure regular staff meetings and clinical review;
- Keeping medical records that included the history, physical examination, and laboratory results; and
- Establishing supervised diagnostic and treatment facilities such as clinical laboratories and radiology departments.[3]

Joint Commission on Accreditation of Hospitals

With the adoption of the minimum standards, representatives of the American College of Surgeons began surveying health care organizations to determine their ac-

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ABBREVIATIONS USED IN TEXT

AMA = American Medical Association
DRG = diagnosis-related group
HCFA = Health Care Financing Administration
PRO = peer review organization
PSRO = professional services review organization

ceptability for accreditation. Additional standards addressing physical plant issues, equipment, and administrative structure led to a broadening of the survey teams. By 1952 the American College of Physicians, the American Hospital Association, the AMA, and the Canadian Medical Association had joined the American College of Surgeons to form the Joint Commission on Accreditation of Hospitals.[3]

Although the Joint Commission initially followed the minimum standards, in 1966 it abandoned this approach in favor of so-called optimal achievable standards.[3] This change occurred primarily for three reasons:

- Most American hospitals were already meeting the minimum standards;
- Medicare set more rigorous guidelines, creating an obligation to respond; and
- The techniques used to assess and improve quality had grown more and more sophisticated.

Avedis Donabedian's classic 1966 article described ways to evaluate the quality of health care and reflected these refinements.[4] He offered a broad definition of quality and recommended that it be measured in three areas: structure—the physical and staffing characteristics of caring for patients; process—the method of delivery; and outcome—the results of care. The Joint Commission and other groups ultimately embraced the structure-process-outcome model, and it is still in use today.

Measuring Quality

For many years the American College of Surgeons and the Joint Commission reviewed medical records to assess quality.[5] From an unstructured and highly subjective form of peer review, these audits evolved in the 1970s into standardized outcome-oriented surveys that also included surgical cases, blood and antibiotic use, and medical support services. The Joint Commission asked that these results be used in credentialing physicians and delineating their clinical privileges.[3]

In 1979 the Joint Commission dropped some audit requirements and replaced them with hospital-wide quality assurance programs. Using a variety of new methods, nonphysicians examined medical records and referred questionable findings to physicians. One new technique was the prospective generic screen in which, for example, reviewers tracked readmissions occurring after a short designated interval or transfers to an intensive care unit as signs of possible problems with quality. Another, the clinical indicator, such as the percentage of women patients on whom pelvic examinations were done, allowed departments to monitor their own performance.[6-8]

New Methods of Measurement

The Joint Commission has recently sought to broaden the scope of "quality assessment and improvement" (formerly "quality assurance") programs. Practice guidelines may help physicians manage patients. Developed primarily by professional societies that use the results of clinical investigations and consensus conferences to recommend standards, the guidelines must cover a wide range of patients and be updated frequently to be effective.

Physician profiling compares practice patterns using epidemiologic data on patients.[9] Investigators have applied this method to cholecystectomy, for example, looking at the number of procedures performed, indications, and complications. Physicians whose profiles stray substantially from the norm might be induced to change their practice habits by their colleagues, the hospital, or governmental agencies.

Adapting a technique called continuous quality improvement developed primarily for industry, the Joint Commission advocated this multidisciplinary approach in its 1988 *Agenda for Change*. This method tries to improve the performance of an entire group rather than identify isolated poor performers.[10-12] All of the workers—administrators, physicians, nurses, housekeepers, clerks—in an emergency department, for instance, might form a task force that would continually analyze and improve care.

Although it concentrates on acute general hospital care, the Joint Commission's mission has grown to include other health care settings—long-term care in 1965, community mental health in 1973, ambulatory care in 1975, and hospices in 1983. Recognizing this expanded role, it changed its name in 1987 to the Joint Commission on Accreditation of Healthcare Organizations. In that year it accredited approximately 5,000 of the 6,500 acute-care general hospitals and 2,800 other health care organizations.[3]

Less than 10% of hospitals gain full accreditation after their first survey; most receive conditional approval based on the need to make prescribed changes. Only 1% or 2% fail to meet requirements that also allow them to participate in Medicare, but even these hospitals usually appeal and ultimately satisfy the Joint Commission's guidelines. Although the value of this approach has not been proved by prospective studies, this regular review seems desirable for internal improvement and to meet the demands of regulators.

Governmental Regulatory Programs

Regulating Health Care

State licensing programs, established toward the end of the 1800s, preceded federal rules; in 1906 national regulation of medication was undertaken by the Food and Drug Administration.[13,14] It was not until 1935 when the Social Security Act set standards for maternal and children's services that health care itself fell under federal supervision. Beginning in 1946 the Hospital Survey and Construction (Hill-Burton) Act required the states to apply minimum codes for new structures built with federal financial assistance. Several years later amendments to the Social Secu-

rity Act directed further state regulatory control over health facilities in return for federal matching funds.[15]

With the passage of Title XVIII of the Social Security Act in 1965 (Medicare), Americans 65 years of age and older received compulsory hospital insurance (part A) and voluntary supplementary medical insurance (part B). To monitor the care of Medicare patients, Congress enacted in the same law a set of rules called Conditions of Participation, which mandated certain principles central to operating a hospital, such as medical staff credentials and 24-hour nursing services, as well as utilization review, which evaluated the appropriateness of admissions.[15] This process established a new level of physician fiscal responsibility.

Under the Social Security Act amendments of 1965, acute-care general hospitals that were accredited by the Joint Commission or the American Osteopathic Association were deemed to have met all the regulatory requirements specified in the Act, with the main exception of utilization review. All hospitals also had to be licensed by their respective states. Hospitals that were not accredited could seek to meet the Medicare Conditions of Participation by electing to undergo a state certification process. Most of these nonaccredited but certified hospitals were then and are still small rural facilities, usually containing fewer than 50 beds.[15]

Professional Standards Review Organizations

The Social Security Act amendments of 1972 also established the Professional Standards Review Organization (PSRO) program to promote efficiency and to try to eliminate unnecessary hospital utilization. The PSRO legislation created a network of physician-run organizations that could grant or deny payment for services provided under both Medicare and Medicaid and that would collect and store basic information on all Medicare and Medicaid patients to create profiles of institutions and individual physicians.[16]

By 1981 PSROs were established in 187 of 195 designated areas in the United States. They never met governmental expectations and were resisted by the AMA, state medical societies, and the states themselves. Finally, it could not be demonstrated that the PSROs actually saved money, and physicians and nonphysicians alike were concerned that the organizations emphasized cost containment over quality.[15,16]

Peer Review Organizations

This disappointment led in the early 1980s to the replacement of PSROs by utilization and quality control peer review organizations or PROs.[15,17] Almost simultaneously, hospitals began to be paid prospectively on a cost-per-case rather than a cost-per-service basis. Peer review organizations are responsible for validating assignments to these diagnosis-related groups (DRGs), reviewing readmissions, reducing unnecessary hospital admissions and operations, and lowering death and complication rates. Reviewers look at a random selection of records of admitted patients and evaluate treatment based on six criteria, known as generic screens:

- The adequacy of discharge planning,
- Medical stability at discharge,
- Unexpected deaths,
- Nosocomial infections,
- Unscheduled returns to surgery, and
- Trauma suffered in the hospital.[15,17]

When PROs identify problems, they may choose a variety of remedies. These include formally notifying an institution or practitioner, requiring continuing medical education, preadmission or more thorough retrospective reviews, referral to medical staff committees, informing licensing and accrediting bodies, and sanctions, imposed only by the Inspector General, such as the loss of Medicare billing privileges.[15,17]

From the start of the program through early 1989, the PROs conducted approximately 6.6 million reviews and denied payment in more than 4% of cases. Practitioners or institutions requested reconsideration of about a third of the denials; denials were reversed some 40% of the time. The PROs identified more than 87,000 physicians with problems with the quality of their care during the same period. Almost all of these problems were resolved through the first few interventions and by the threat of sanctions, so that only 109 physicians were actually referred to the Office of the Inspector General. Although some might regard this small number of referrals as a sign that the PROs are ineffective, it more likely reflects the success of less severe measures in improving the quality of care.[15]

The PROs clearly emphasize quality and focus more on outcome as opposed to structure and process than did the PSROs, but they have not been immune to criticism. Some see the criteria they use to identify problems in quality as too insensitive, and others complain that intrusive PRO bureaucracies generate more paperwork than actual improvement in a flawed system.[18]

Responding to these criticisms, Congress asked the Health Care Financing Administration (HCFA) in the late 1980s to sponsor a study by the Institute of Medicine of the National Academy of Sciences on quality assurance for Medicare.[15,19] The study concurred that PROs were limited in scope and called for restructuring them and implementing yet another program, the Medicare Program to Assure Quality. Charged with updating the conditions of participation and encouraging the Joint Commission to modernize its quality improvement methods, this effort would continue to use existing PROs, but would direct them to look even more closely at outcome in evaluating institutions and practitioners.[19]

Recent Legislation

The most important law in recent years to address quality was the Omnibus Budget Reconciliation Act of 1989, which instituted physician payment reform in the Medicare program.[20] This grew out of a study of new payment methods authorized in 1985, leading one year later to the Physician Payment Review Commission. The Com-

mission recommended that Medicare's "customary, prevailing, and reasonable" reimbursement schedule be replaced by one based primarily on resource costs related to a relative value scale. Undoubtedly this will change practice patterns and thus affect both cost and quality of care.[21-25] At the same time, new efforts in utilization review and quality assessment will be needed. These efforts will be aided by new data about individual and institutional practices that will help physician and hospital profiling to an extent not previously possible.[21]

The Omnibus Budget Reconciliation Act also authorized greater federal support for health services research and set up the Agency for Health Care Policy and Research. This agency replaced an existing office and highlights the government's interest in improving the outcome of medical treatment by supporting studies of health services and practice guidelines.[26]

Quality Improvement Initiative

Practice guidelines may have their first major effect as a result of the Health Care Quality Improvement Initiative proposed by the HCFA in 1992. This will attempt to steer PROs away from generic screens that have led to conflicts with physicians toward a cooperative approach based on the principles of continuous quality improvement. It will have three elements: a national history claims file made up of all claims paid by Medicare; a uniform clinical data set, which will provide information on 10% of discharged patients; and a patient care algorithm system based on clinical guidelines.[27]

The aim of the Quality Improvement Initiative is to apply the patient care algorithm to information provided by the claims history and data set. This will allow the PROs to both screen cases and describe how well the care conforms to published guidelines. They will then inform physicians and hospitals of these profiles, work with them to analyze areas of possible improvement, and assess changes as they occur.[27] This approach is still in its infancy, with only six PROs currently active in a pilot test of the uniform clinical data set and an algorithm system that has few guidelines written. The initiative will need more funding, and it is not certain whether physicians or hospitals will embrace it.[28]

Methods of Enhancing Physician Qualification

While the federal government has tried to influence physicians indirectly through cost containment and quality improvement programs, the states generally regulate more directly by licensure, relying on standards set by professional organizations. Developed with the support of the AMA, the National Conference of State Medical and Licensing Boards was formed in 1891 and the National Board of Medical Examiners in 1915.[1]

All states require applicants for a license to have graduated from an accredited medical or osteopathic school with special provisions for graduates of foreign schools. About two thirds also insist on a one-year internship; a passing grade must also be achieved on a standardized examination. To renew a medical license, physicians in 24 states now must complete a prescribed number of hours in continuing education.[29]

Once licensed, physicians are not limited to any specific field of medicine and thus can practice in areas for which they have little or no training. Many physicians, however, have completed residencies and become certified by one of 23 specialty boards after passing an examination in that discipline.[30] Although certification was once permanent, 15 of the 23 boards have adopted or will soon adopt time-limited certification and a recertification process.

Because state hospital licensure holds institutions responsible for the care provided under their authority, hospitals must be assured that physicians who practice within them are qualified. At one time hospitals' only obligation was to make certain that physicians had valid medical licenses, but other criteria are increasingly being used to judge their qualifications. Among these are board certification and recertification, complaints made to state boards of medical examiners, and reports from the National Practitioner Data Bank.[31]

Created by the Health Care Quality Improvement Act of 1986, the National Practitioner Data Bank contains information on payments made by malpractice carriers to settle claims against physicians, as well as actions taken against physicians by hospitals and other health care organizations. Since 1990 medical staffs have had to provide to and solicit information for the data bank to obtain credentials and grant privileges.[32] The bank registered nearly 800,000 queries in its first year. Nearly 20,000 adverse actions and malpractice payments made were reported to the bank during the same period. The actual number of adverse actions is uncertain. It is not known if or how the required queries to the data bank were used,[33] nor if physicians regard this and other methods of enhancing their qualifications useful or necessary.

Liability Litigation and Underwriter Demands

Physicians in the United States once had few fears about malpractice suits and paid little for malpractice insurance. After World War II, however, the number of suits and the cost of premiums rose dramatically. Responding to this in 1971, President Nixon ordered a study that found that the increase in claims had led insurers in many states to boost charges for policies to an unaffordable level or to refuse altogether to write malpractice insurance.

Equally striking was the influence commercial carriers were beginning to exert over quality of care. A number of insurance companies in California dropped hospitals and forced them into a group contract with a single firm, under which hospitals had to report incidents that might adversely affect the care of patients. The system, a forerunner of today's risk management programs, detected many problems and prompted many innovations, including wrist bands to identify patients in hospital and bed rails to prevent falls.[34]

Concerned about rising malpractice claims and premiums and wishing to find an alternative to tort law, the Cal-

ifornia Medical Association and the California Hospital Association commissioned a study to explore the extent of disability and death caused by adverse events. One type of event was an untoward drug reaction. Having identified such an occurrence, the investigators tried to determine its cause. Among the records studied, they found adverse events in approximately 5% of the total, of which 82% was attributed to treatments or procedures, 15% to incomplete diagnoses or treatment, and 2% to inadequate preventive measures.[35]

Extrapolating data from about 20,000 reviewed charts to the state's total number of patients admitted to hospital in 1974 suggested that 140,000 adverse events had occurred. From the standpoint of liability, it was possible to fix blame for only 17% of these episodes on medical or surgical fault, implying that the disabilities or deaths in the remaining 83% would not be compensated under the tort system. And there are doubts about whether even those patients injured by physician negligence would receive restitution because only one in ten such persons sued and was eventually compensated in California in 1974.[35]

Other studies also have shown that malpractice litigation is an insensitive way of uncovering deficiencies in quality.[36-38] Less clear is the extent to which the real or perceived threat of malpractice suits deters health care professionals from negligent behavior, even though it has prompted many to practice defensive medicine.[39-41] Could following practice guidelines simultaneously reduce negligence and open the way for a reduction in the money spent on malpractice insurance, estimated to be 15% of the total expended on physicians' services? That remains to be seen.[42-45]

Changes in the Organization of Medical Practice

Medical practice was once dominated by solo general practitioners who operated as independent businesses and expected limited financial return. That physicians had relatively few interventions to offer justified the leanness of this return. They dealt with most patients face-to-face and usually at the bedside, consulted other physicians infrequently, and were responsible primarily to themselves. Such practitioners formed a majority of the AMA, and its political stance opposing governmental intrusion reflected the professional and economic autonomy of its members.[46]

The landscape of American medicine has changed dramatically. Specialists working in groups dominate solo general practitioners. Financial rewards from both fee-for-service billing of third-party payers, including federal and state governments, and from employment by large medical corporations are more generous.[47] Given practice arrangements and fiscal concerns, it is not surprising that practice habits and treatment results are being scrutinized far more often.

The trend toward corporations has led to a decrease in physician autonomy and an increase in competition. Hospitals and other health care institutions vie in public by comparing costs and styles of providing care. In the future, it is likely that they and their practitioners will compete increasingly on the basis of outcome. This will further encourage the federal government and the Joint Commission to create profiles of physicians.

One can also see the role competition will play by the interest in managed care.[48,49] Regardless of the form they take, managed care plans compete with one another to provide care that is appropriate, cost-effective, and appealing. Presumably quality, measured primarily in terms of clinical outcomes and patient satisfaction, will be an important, if not the most important, element in this appeal. Thus, quality and cost must be continuously assessed and improved if the plans are to remain competitive.

Future Prospects

Greater concern for cost than for quality has marked many of the older regulatory efforts described here. This focus may lead to undesirable results. For example, the use of copayments and deductibles to decrease utilization and thereby lower costs may worsen health if both needed and unneeded services are reduced. To have a positive effect, policies should provide the following:

- Limit services that are of little or no benefit to patients.
- Encourage less costly and more effective care,
- Ensure access to that care, and
- Foster integrated health care systems that can provide beneficial services more efficiently.

Profiles and practice guidelines will supplement if not replace utilization review, case-by-case analysis, and the identification of outliers in efforts to control quality and help physicians improve their practices. This will be accomplished only with a large federal investment in outcomes research, user-friendly data services, and education. Medicine is quickly approaching a crossroads at which physicians must choose between accepting these new approaches and submitting to even more external control from which neither they nor society is likely to benefit.

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Commentary

Will Managed Care Alter the Art and Soul of Medicine?

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Recently a colleague in family practice received a letter from an irate patient in which she complained that the physician was "only interested in practicing cost-effective medicine." In the context of a contemporary medicine "good news-bad news" story, this complaint illustrated a good news component: the physician obviously was doing an efficient job as a gatekeeper in the milieu of managed care, and the bad: a patient was obviously unhappy with the apparent roadblocks that her primary care physician interposed between her and whatever it was she thought she needed from the health care system in which she was enrolled.

Is the art of medicine in danger of being changed by managed care? To many long-time practitioners, the rules and regulations that are typical of the various health maintenance organizations (HMOs) and independent practice associations seem to be infringing on physicians' practice styles, or their art of medicine. Pediatricians accustomed to seeing babies every month during the first year of life find that HMO rules limit the frequency to far fewer visits. A physician like the one portrayed in Sir Luke Fildes's famous portrait spending an entire night by the bedside of a critically ill child would probably have a difficult time receiving fair recompense from an HMO, which might argue that a single dose of a broad-spectrum antibiotic intramuscularly would have made this prolonged detention unnecessary. Internists who provide annual physical examinations to all patients who request them find that there are distinct limits on the frequency of these and on such things as electrocardiograms, chest x-ray films, and biochemical tests. Obstetricians accustomed in past decades to having new mothers stay in the maternity ward for as long as a week now watch them leave much earlier, often within 24 hours after vaginal deliveries, or 72 hours after cesarean sections. When short stays were initially introduced by HMOs, the nursing staff in many hospitals spoke against these limited postpartum stays; yet their fears of increased morbidity failed to materialize, and by now, everyone is aware that early discharge is safe and helps limit nosocomial infections.

Many physicians think that the relatively low fees provided by managed care organizations restrict their ability to provide the type of care that they would like to provide; for example, there is less time to practice the art of medicine in such services as counseling. It is true that such types of care are not recompensed at a rate that makes it worthwhile for physicians to spend the required length of time to do an effective job. This unfortunately follows a pattern present in medicine for ages: cognitive services have long been underfunded, and this practice has not changed with the advent of managed care. Certainly it is more cost-effective to understand a patient's angst that is causing his backache than to refer the patient for a magnetic resonance image of his spine. Perhaps with more practicing physicians achieving managerial status in HMOs, more generous funding will be afforded physicians who want to ply their art of medicine using the old-fashioned but still useful "history and physical."

But the shadow that managed care is beginning to cast over the souls of physicians is a concern. Physicians, who have survived the competition of medical school and postgraduate training and who expect to practice on their own terms to achieve the fulfillment they feel they deserve, are shocked to see the loss of autonomy caused by managed care. The old maxim that one need only find the community in which one wants to live, then practice ethical and high-quality medicine and success will be assured is not as assured as it once was. In this new era in which the number of board-certified specialists far exceeds the number of primary care physicians, managed care organizations find that they function most efficiently with exactly the opposite mix. Brilliant plastic surgeons and neurosurgeons, for example, discover to their dismay that the community of their dreams does not have room for them now and may never have a place in the foreseeable future.

There is no easy solution to the problem of underutilized specialists in the new managed care environment. In some instances, specialists can do competent primary care and can meld into the system; too often, however, they find themselves unable to cope with the routine problems of primary care medicine and, as a result, refer patients too frequently to other specialists. In a managed care system, physicians who have a high volume of referrals for problems usually handled by primary care physicians do not win popularity contests.

Even the specialists who are "chosen" to work with the gatekeepers in a managed care system find all too of-

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ten that they must bow to the wishes of the primary care provider. Technology that specialists have become accustomed to using may be unavailable if a primary care provider deems it too expensive. Or a gatekeeper may make arbitrary judgments about the number of visits that a patient can make to a specialist. Specialists not used to second guessing from less knowledgeable colleagues may find this most distressing emotionally.

Managed care appears about to become a major player in the future of health care in the United States. The Clinton Administration suggests that this will become the major if not the only option. Physicians who are certain that this is a type of health care they will not practice will seek a viable alternative. But whatever the outcome, the face of American medicine, its art, and perhaps its soul, will likely be changed forever.

Responses

Defending the Art

CONTEMPLATING THE FUTURE of medical care is similar to staring into a foggy forest from which loud sounds emanate. We know there are powerful forces therein, but we cannot discern exactly whether they will oppose—or possibly help—us.

Virtually every scenario for health care reform in the United States is based on variations of managed care, whether health maintenance organizations (HMOs), preferred provider organizations, or independent practice associations. Soon independent medical practitioners will be museum pieces.

How will such practice arrangements affect the "art" of medicine? If the design and implementation of future health care plans are left to politicians, insurance company gurus, and the occupants of corporate boardrooms, the result will indeed be grim. A colleague recently told me of his experience with an HMO that required that he see a patient every 12 minutes. In my own state, a government-designed universal access plan would mandate seeing a large number of patients at capitation rates set so low as to preclude many clinical services.

Politicians and business directors view patients as differing little from small appliances, capable of being rapidly processed and shuffled, if need be, from one "provider" to another, possibly by way of a "gatekeeper." Any notion of medicine having an artful dimension is foreign to such health care reformers. They view medicine merely as a branch of engineering.

Before proceeding further, I offer my own definition of the art of medicine. This is the dimension of compassion and soulfulness of our clinical profession. It is our artfulness as clinicians that allows us to step beyond scientific observation and therapy to perceive the hurt or longing in our patients. Practice of the art requires time, patience, and privacy. The process cannot be rushed; a time clock is its enemy. The art allows us to lend encouragement in a difficult recovery process or to ease the travails of a hopeless illness. The art of medicine is our walk with each of our patients through the valley of the shadow.

For physicians so inclined, clinical practice is the career for which no substitute can be imagined. The art of medicine is an inseparable component of this professional life. In personal experiences with physicians in a highly structured British National Health Service, I have seen and experienced the art of medicine practiced undiminished. Similarly, in the Army Medical Corps, I have seen dedicated physicians bring the art of medicine into dispensaries, stockades, and emergency wards. Tired medical residents repeatedly show me their stamina by never relinquishing the art, no matter how late the hour or how disheveled the patient.

By their nature most physicians will insist on practicing the art as well as the science of medicine whatever the clinical setting. The ease with which this is accomplished requires wisdom at every stage of design, planning, and administration of health care plans. Reimbursement and practice space may be negotiable. The proper practice of the art of medicine is not. An early colonial American flag pictured a serpent and the motto "Don't tread on me." Quite possibly the serpent from our own caduceus may need to be similarly used to warn those organizers of medical care who would seek to deny physicians the privilege and obligation to practice humanely and thus artfully.

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Physicians' Responsibility Under Health Care Reform

MARVIN AUERBACK, MD, asks if managed care will change the art and soul of medicine? The answer is, "not necessarily."

The art and soul of medicine have been threatened before. For example, a prominent physician wrote, "The most common criticism made at present by older practitioners is that young graduates have been taught a great deal about the mechanism of disease, but very little about the practice of medicine—or, to put it more bluntly, they are too 'scientific' and do not know how to take care of patients." This quotation is from Francis Peabody's famous essay, "The Care of the Patient," published in 1930.[1] We can take some solace from the realization that concerns over the art and soul of medicine are not unique to our time.

Today, the engine of change is not science but cost containment. It is a pervasive part of our everyday life and will be more so in our future. The Clinton reform proposals, for instance, would bring the rate of health care cost increases down to the level of increase of the gross national product by 1998 and hold it there. Assuming, for the sake of discussion, that the coming health care legislation embodies this intent, then physicians and society will be operating under a new constraint—a fixed

budget. New treatments, newly discovered needs, even new diseases can no longer be attacked by increasing the share of resources allocated to health care. More resources for one item can be developed only by reducing the resources spent on other items. Since the dollars available through health alliances will be constrained (rationed), care may also be constrained (rationed) unless the system becomes more efficient.

Under a fixed budget, the amount of health care available to the population becomes a direct function of the efficiency and effectiveness of the health care delivery system—how much bang is available from each limited buck. Ineffective delivery systems mean more waste and consequently less care. Physicians, as well as hospitals and others in the health care field, will now have a direct responsibility to society to organize systems to provide the best and most efficient care this fixed budget will allow. Physicians must accept the responsibility to be active participants in the design and management of these systems, rather than leave this to those with less understanding of health care delivery. Physicians must also show that they are a profession interested in the well-being of all Americans, as well as their own patients, and that they can do a better job under the constraints of fixed resources than bureaucrats, politicians, and other experts.

If physicians passively participate in systems in which they simply accept fees, or even negotiate fees, but accept no responsibility for making the system work, they will lose control over their practices. The payer—be it an insurance company or a single-payer government scheme—that takes the risks for access, costs, and quality must protect itself against these risks through micromanagement of physicians' practices. If, on the other hand, physicians accept responsibility and risks, control of the delivery system should lie with them as it does in some programs today.

I would say to Dr Auerback that if physicians manage managed care, the art and soul of medicine have a better chance of being preserved than if that management is turned over to others, regardless of how well-intentioned the others may be. The amount of art and soul that can be built into these systems will depend on the values of the physicians, the benefit to patients of these values, the degree of influence physicians have on the system, and the ability of the system to free up resources to support these desirable practices.

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Who Will Manage Patient Care?

MARVIN AUERBACK, MD, provides a cogent argument to support his conclusion that "the face of American medicine, its art, and perhaps its soul, will likely be changed forever." Although there are many reasons for the changes, few practicing physicians would deny that managed care is a major cause of the alterations in health care delivery and practice styles outlined by Dr Auerback. Few would also deny that major reform is needed.

Costs that are out of control—rapidly approaching 14% of our gross national product—and limited and unequal access to health care are problems that trickle down to shrink the pocketbook of all Americans and the quality of life of many. So the question we must ask is not should we fix the health care system, but how? And can we do it without threatening, perhaps destroying, the physician-patient relationship, which is so vital to the well-being of patients? Managed care has yet to provide an answer to either question.

Managed care systems are not homogeneous, but they are all based on the premise that medicine is and should be a business. This premise threatens the mutual confidence and trust between patients and physicians, both essential ingredients of successful patient care. This premise and the operational rules it requires threaten the autonomy of physicians as they make even minor decisions in day-to-day patient care and, more important, the autonomy of sick patients as they struggle to decide their own fate.

"Case managers" play an important role in managed care systems. They are seldom physicians, they never see patients, and they have no responsibility for the welfare of patients. They have a responsibility to their employer: the managed care plan. Their job is to save money for their employer by micromanaging physicians' decisions and, in turn, patients' illnesses. Not long ago I admitted a patient to hospital for placement of a Tenckhoff peritoneal catheter for permanent dialysis. Sometimes we can admit patients for this procedure and send them home in the evening. Sometimes it is in their interest to stay overnight. In this instance the patient had more pain than usual, along with severe vomiting, and we kept her an extra night. I received a call from a case manager at the patient's insurance company saying that he was "disallowing" the extra day's stay. I asked the person if he knew what a Tenckhoff catheter was, if he had seen patients with them, if he knew the possible complications of catheter placement, or if he had ever seen a patient with end-stage renal disease, let alone cared for one. The answer to all of the questions was "no." Not once in our conversation did he ask whether or not the patient benefited from the extra day in the hospital or whether or not she had recovered from her pain and vomiting.

The emphasis on the bottom line is placing pressure on physicians to act more like businessmen and businesswomen and less like patient advocates. Terms like competition and marketing are becoming required vernacular. We are being asked, indeed forced, to make bedside decisions based not on what is best for our patients, but on what is best for insurance companies and managed health care plans.

The practice of medicine is not in the most basic sense a business. Our job is not to sell goods or services, whether patients need them or not; nor should we be expected to make decisions about patient care based on profit mo-

tives. Our responsibility is to provide patients with health care and to act as their advocate in time of conflict with institutions and agencies that threaten the quality of the health care we provide. This responsibility should not be dependent on any expected financial gain. It is a hallowed tradition that is essential to our patients' well-being. It is the reason for our existence. It is the "soul" of medicine, and if the "soul" is changed, as Dr Auerback suggests, it will be our patients, not ourselves, who will suffer the greatest loss.

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Overcoming Managed Care Blues

YES, AS SUGGESTED IN Marvin Auerback's lucid essay, managed care does threaten to harm the soul of medicine and blight our spirits . . . but only if we let it. As we adapt to monopolistic, Big Brother medicine, my antidote for our melancholy is to look for honest pleasures in our lives and build on them. Our cardinal pleasure is the one that we should cultivate the most, that which comes from working through clinical problems and making the best decisions for our patients. This well will never run dry. In parallel, we can seek out and do new and different things in our practices. Life is change; change excites. Take a course in echocardiography or come to grips with likelihood ratios and the probability game.

We have come to depend too much on reports about our patients gathered by others. We cannot see our patients for the data. The remedy is to do more things that are concrete, immediate, and palpable—touch, take our patients' blood pressure measurements ourselves, look at x-ray films ourselves. This can give us a sense of command, understanding, and closeness to a patient that can be gained in no other way.

We are too insular. There is much to gain by going outside medicine and viewing the world through the spectacles of others. Regular participation in nonmedical discussion groups can be salutary for physicians. By going outside, we get inside. And we have our families, hobbies, and sports—tennis, anyone?

Cheer up, comrades, there are shoals ahead, but our lives and managed care do not have to be unmanageable.

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Commentary

Health Care
Transformation of Systems and Soul?

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There is little question that our health care system is not fully satisfying our needs. In modifying it, our often short-sighted economic goals, as well as strong emotions and biases, seem to eclipse long-term vision and respectful compromise. In the hospital corridors and in the media we hear, read about, and experience health maintenance organizations, preferred provider organizations, independent practice associations, and capitation. Specifics are often emphasized without reference to vision, goals, or objectives other than saving money. Several important concepts seem unrecognized or unreported, yet are critical if a sustainable health care program is to be created.

The present state of health and health care delivery is not simply a crisis of the system. It is a crisis of how we view our world and our place in it. It is not simply an issue of concern when we are sick, but relates to every moment of our existence. It is more than a problem of access to health care professionals or facilities or a problem of rationing money or defining which services are to be allotted to whom and when. It is a dilemma requiring us to accept the finite nature of our natural resources and their present imbalanced distribution. It is a collection of questions not solvable by trading high-tech disease interventions for simpler, less expensive alternative or preventive measures, but a matter of accepting individual responsibility for our thoughts, feelings, and actions. The crisis will not be rectified by government-provided universal health insurance coverage, employer-sponsored coverage for employees, or capitation versus indemnity plans. It is an issue of compassion and how we view our relationship to other human beings and their suffering. It is not just a matter of resolving ethical dilemmas related to, for example, tissue transplantation, compromised newborns, or the elderly, but a need to confront our concepts of death and dying and their effect on our health care practices and the living of our lives.

We need more than a new health care system; we need a new vision, a new meaning of health. We need a perspective that will bring fresh meaning to the dialogue and that will infiltrate our system of health practices and affect the ways in which we respond to these evolving times.

While it is difficult, it is useful to identify specific philosophic issues and values that must be engaged, not solved, if we are to create an accessible, sustainable, balanced health care system. These issues include the following:

- *We must acknowledge the constraints of the limited resources available to provide health care in the context of our planet's finite resources.* We live thanks to the only oxygen-containing atmosphere, potable fresh water, and fertile topsoil for trillions of miles. These resources are strictly limited and their interactions complexly intertwined. From this global perspective, the reality that we have to live within certain boundaries, balance destruction with construction, and consumption with preservation, becomes abundantly clear. From ozone to water, carbon dioxide to garbage, oil to money, our existence demands limits, balance, and compromise. We know that we cannot continue to demand from our health care system results or developments that are limitless. To seek to determine the structure and function of a health care system in the absence of fundamental understanding of the philosophic beliefs and values inherent in society is like trying to create a business plan, a product line, target audience, and quarterly profit for a company that has not yet accepted a corporate vision. The vision here addressed is one of limits.
- *The individual and the extended community must accept responsibility for health-related decisions and behaviors.* Our health-related challenges and the quest to reform the health care system call on us to search for wisdom and meaning. Our health problems and the associated human suffering, like our environmental, economic, and geopolitical problems, are interconnected and global in magnitude. We cannot pretend that all problems with our health care system are the fault of practicing health care professionals. In fact, the circumstances of our present state of health and illness are a response to the demands of the dominant and controlling elements of our society. We are all responsible. So as we remodel the system we are creating a new philosophy of health and an evolving philosophy of living. Here we can apply our efficient and successful western scientific thinking and ap-

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proaches in concert with the wisdom and practices of other sources. The knowledge and practices of other cultures, as well as preventive, mind-body, or alternative and complementary forms of care can be useful additions to our health care system. For new diagnostic approaches, treatments, lifestyle changes, and behavior modifications to become health generating, socioeconomic and cultural beliefs and attitudes will gradually need to change through research, education, and example. As with allopathic practices and remedies, alternative or complementary forms of care become more accessible when expanded insurance benefits make them covered services. But accessibility is not the only issue. These practices must be used appropriately, scrupulously, and with compassion, as with technologic and allopathic practices.

If each person recognized and accepted the importance of his or her own decisions related to health, the monetary savings would be astounding. Inappropriate diet, overconsumption of alcohol and other addictive substances, smoking, and sedentary lifestyle, if moderated or eliminated, would likely save more money and create more health than could possibly be achieved from changing the system of medical care. Yet it seems that most people do not know this, deny it, or prefer medical, pharmaceutical, or surgical intervention to modifying their behavior.

The responsibility that each person must accept for a balanced way of life is extended to the community at large. If the individual and the community are to take responsibility for their health, they must have the tools to do so. Community-based decisions must be made and justly applied and administered. These decisions cannot be made at the bedside nor based only on financial considerations but must address individual, cultural, social, and philosophic concerns as well. These decisions will be inadequate if they do not acknowledge the deeper meaning of our lives. To the extent that they are consistent with our values and beliefs, they will provide healing in and of themselves by bringing together the scientific and the spiritual.

Not only the public but the medical profession must responsibly support the integration into our evolving health care system of those practices shown to be effective. Health care must be applied and distributed within the context of an overriding strategy that supports education, prevention, and access while assuring a balance between individual and societal wants and needs.

• *Our western concept of death profoundly affects the health care system.* We tend to see death as an end, a terminal event, a tragedy, a failure, and a loss. This viewpoint helps explain why a high percentage of the health care dollar is spent in the first and last months of life. In the eastern traditions, death tends to be viewed as leaving or dropping the physical body. It is as much a beginning as an ending and is seen as another step in the mysterious journey on which the bodily existence is only a part. Philosophically confronting dying and death in discussing the health care system and what "drives" it is admittedly a sensitive and difficult challenge. As we face our perceptions of death, our living will benefit, for it is in facing our inevitable and unpredictable deaths that we truly engage our lives.

For productive, positive change to occur, a vision of our destination and the road to it is essential. This vision can result in the evolution of a system that is relevant, responsive, integrated, accessible, and sustainable. This does not imply that no difficult decisions will be necessary, that no compromises will be required, or that everyone will be satisfied or happy with the results. It does, however, help to create a set of ground rules that can be accepted by those who are responsible for adapting our present health care system to the needs of our time and situation. A broad philosophic vision can affect the response to changes in both the health care giving and receiving communities. No issue, thought, feeling, or action escapes being health creating or health destroying. Herein lies the power of the health and healing metaphor and the pivotal value of creating a system that serves each person, our communities, and our world.

Editorials

Ebb and Flow of the Circulation

THE CIRCULATION OF THE human body has fascinated diagnosticians and scientists since scientific thought was introduced into the practice of medicine. The assumption of functional concepts by dint of morphologic observations spawned considerable controversy in the early 17th century. One of the early controversies in medicine was initiated by the publication of *De Motu Cordis* by William Harvey in 1628. Harvey's notion of the circulatory movement of blood with passage through the lungs propelled by a contracting heart disputed the Galenic concept of the ebbing motion of blood with passage through pores from the right to the left sides of the heart. In turn, the concepts of physiology derived from anatomical observations proffered by Harvey were ridiculed by Descartes and associates using equally tenuous concepts. A lack of experimental methods for testing physiologic hypotheses perpetuated inevitable controversies surrounding inconclusive predictions of circulatory dynamics based on morphologic observations alone.

In this century, controversies regarding cardiovascular functioning have been resolved by the array of sophisticated techniques available for precisely measuring the circulation, and, interestingly, these direct measurements have supported many of Harvey's concepts. The widespread use of Doppler ultrasonography for the past decade has permitted the direct observation in humans of hemodynamic phenomena demonstrated previously in animals using flowmeters.[1]

In the current issue of the journal, McDonnell and coworkers have reviewed the salient physical principles and the application of flow-sensitive (encoded) magnetic resonance (MR) techniques for imaging and quantifying blood flow.[2] This technique is evolving as a method for providing spatially precise measurements of blood flow at all sites in the cardiovascular system.

Even before the first magnetic resonance images were produced, MR techniques were used to measure flow velocity in tubes.[3,4] Because the MR signal is modified by blood in motion, it was recognized early that this new modality had considerable potential for the investigation and diagnosis of cardiovascular diseases.[5,6] The unique signal generated by flowing blood compared with stationary tissue enables the portrayal of cardiovascular structures without the need for contrast media to outline the blood pool.

As discussed in the review by McDonnell and associates, the unique signal provided by flowing blood can be exploited to produce noninvasive projectional images of the blood vessel in which the arteries (MR angiography) and veins (MR venography) can be viewed separately. Because the imaging data are acquired three dimensionally, the reconstructed image can be rotated in any direction to provide many viewing angles. Although the spatial resolution of MR angiography is less than that achieved by x-ray angiography, MR angiography is reaching clinical acceptance for evaluating carotid arterial stenoses and intracranial arteriovenous malformations, detecting occult intracranial aneurysms, and identifying the presence and extent of intracranial venous thromboses. At a few centers, MR angiography is also reaching clinical acceptance as the preferred technique for evaluating intrathoracic and intra-abdominal venous thrombosis, hepatic arterial and venous integrity in patients before and after hepatic transplantation, renal arterial stenosis in suspected renovascular hypertension, and distal limb circulation for limb salvage in patients with advanced peripheral arterial disease.

The initial application of new imaging procedures was to depict form and structure. In this regard, the major clinical use of flow-sensitive MR techniques has also been to depict vascular form and structure (MR angiography). Substantial research has also been directed over the past few years to realize the enormous potential of flow-sensitive MR techniques for investigating blood flow and other functional aspects of the circulatory system.[7]

The investigation of the use of flow-sensitive MR techniques has to some extent followed the path of Doppler ultrasonography, but it has also helped quantitate blood flow beyond the scope of Doppler and color flow mapping ultrasonography. Doppler ultrasonography probes the velocity of flow in a region with a small volume, but it cannot actually measure the volume of flow. The disadvantage of MR over ultrasonography at present is inferior temporal resolution. The greater sampling rate of ultrasonography can be expected to better identify the peak velocity of flow across vascular and valvular obstructions and thereby to predict more reliably the gradient (using the modified Bernoulli distribution) across an obstruction. On the other hand, the capability of the MR method for accurately measuring volume flow in either the antegrade or retrograde direction permits the precise measurement of the volume of valvular regurgitation, the volume of left-to-right shunts, and the volume of flow separately in the right and left pulmonary arteries. The temporal resolution of the flow-sensitive MR techniques can be expected to improve now that the echoplanar technique is being introduced at many centers in the United States and Europe. Echoplanar MR can acquire images at 50-millisecond intervals (sampling interval).

The clinical uses of velocity-encoded MR have not yet been established because the technique has been in existence for only a short time. Because the technique is similar to that of Doppler echocardiography, there has been a tendency to use it in a manner akin to the clinical uses of Doppler techniques. Because of lower costs, universal familiarity, and the ubiquity of Doppler echocardiography, it is highly unlikely that flow-encoded MR techniques will displace Doppler imaging from its current clinical role. Velocity-encoded MR should be considered as a method to provide quantitative hemodynamic data not available with current noninvasive techniques. In this re-

gard, velocity-encoded MR can measure diastolic retrograde flow in the ascending aorta. The technique has provided an accurate direct measurement of the volume of aortic regurgitation in patients with this disease.[8] Moreover, sequential studies in a group of patients with isolated aortic regurgitation have shown excellent interstudy reproducibility of the measurement.[8] This finding indicates that velocity-encoded MR could be used as a reproducible method for monitoring the volume of regurgitation over time and documenting the effectiveness of pharmacologic interventions intended to reduce the severity of regurgitation. Preliminary results of the use of this technique to assess the effectiveness of an angiotensin-converting enzyme inhibitor in several patients with aortic regurgitation demonstrate effectiveness of the drug in some but not all patients.[9] Although imaging studies are not currently applied for this purpose, a technique for precisely quantifying the hemodynamic effect of a drug might be used in the future to define the therapeutic regimen in patients with valvular regurgitation.

In another recent paper, the feasibility of using velocity-encoded MR for measuring blood flow in coronary arteries was indicated.[10] In normal coronary arteries, administering a vasodilator caused a substantial increase in the velocity of blood flow. On the other hand, velocity-encoded MR showed no increase in flow velocity in response to the vasodilator in coronary arteries with severe stenoses. Velocity-encoded MR is the only method for measuring blood flow in native coronary arteries; consequently, a unique use would be to identify arteries with hemodynamically important stenoses.

A unique application in congenital heart disease is suggested by another recent observation. The use of velocity-encoded MR to measure flow in the proximal and distal descending thoracic aorta in normal subjects indicated a small decrease in flow volume from proximal to distal aorta consistent with normal runoff into the intercostal arteries.[11] In patients with moderate to severe coarctation of the aorta, however, flow increased substantially from the proximal to the distal aorta, due presumably to retrograde flow in the intercostal and other arteries recruited into supplying blood to the lower body. Thus, a unique application of velocity-encoded MR is to quantify collateral flow in patients with coarctation of the aorta to predict the neurologic risk of cross clamping the aorta at the time of surgical repair.

In addition, velocity-encoded MR provides a method for assessing the cross-sectional and longitudinal flow pattern in the aorta. It will be intriguing to determine if flow patterns vary with age and between normal subjects and those with atherosclerosis. These techniques also provide a window on the vascular aging process by permitting repeated noninvasive assessment of arterial compliance.[12] Magnetic resonance techniques will undoubtedly be used to investigate the variation in aortic compliance associated with the aging process and in response to exercise regimens and pharmacologic interventions.

Whereas imaging techniques have been focused on the examination of abnormal anatomy, it is clear that the strength of this new technology for use in the cardiovascular system should be developed and appropriately applied to quantify abnormal cardiovascular function. Its eventual role will likely depend on establishing the clinical importance of the unique information it can supply.

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Needle Biopsy of Probably Benign Nonpalpable Breast Lesions

THE BOTTOM LINE of screening mammography is that it can reduce mortality from breast cancer by about 30%. This is accomplished at a cost of about $30,000 per year of life expectancy gained—$15,000 to $125,000, depending on factors such as statistical methods, age of the women, the addition of breast physical examinations, and the decision to do biopsies of probably benign lesions.[1-3]

In women undergoing routine screening mammography—soon to be most women in this country—about 50% of all biopsies are done for nonpalpable or occult lesions (whereas 20% to 40% of all breast cancers will be nonpalpable). These occult masses or microcalcifications are the subject of considerable controversy. Mammographers argue about when to take a biopsy of the commonly identified slightly suspicious, or probably benign, lesions. When biopsies are taken of these nonpalpable lesions, there is difference of opinion about whether this should be done surgically after mammographic localization, or stereotaxically using fine-needle aspiration or large-core-needle techniques.

How frequently a biopsy is recommended and performed on probably benign nonpalpable breast lesions depends almost entirely on the skill and philosophy of the radiologist interpreting the mammogram and the medical malpractice environment in which he or she works.[3] Positive predictive values (PPVs) for carcinoma on biopsies of such occult lesions in large series in the United States are generally 20% to 30%, with a range from 15% to 40%.[3,4] Corresponding PPVs in European series are considerably higher, ranging as high as 70%.[4] These values generally increase ("improve") as mammographers become more experienced and the published series become larger.[3-7] Between 20% and 40% of nonpalpable carcinomas are ductal carcinomas in situ, and the pathologic diagnosis and surgical treatment of this disease are the subject of further controversy.

Elsewhere in this issue, Shields and co-workers give their experience in the biopsy of mammographically detected nonpalpable lesions.[8] These authors had an overall PPV of carcinoma of 19% and a PPV of only 7% in women younger than 50. These low figures, and the relatively small number of biopsies (125), suggest that this was an early experience with suboptimal mammographic skill. Unfortunately, there is no ideal PPV for such lesions, and a tradeoff exists between costs and benefits.[1,4] It is important to realize that an overall PPV of 20% does not mean that an individual patient has a 1 in 5 chance of having carcinoma. Many nonpalpable lesions are highly suggestive of malignancy, and an overall figure of 20% indicates that biopsies are being done of individual lesions that are much less suggestive of cancer than 1 in 5. Those few carcinomas that are observed rather than undergoing immediate biopsy are not "missed." Rather, the 6- to 12-month delay in diagnosis should be viewed in the context of the normal 8- to 10-year life span of breast carcinoma before it becomes palpable. Finally, many nonpalpable calcifications are ductal carcinomas in situ, and, as in the case of in situ prostate carcinoma, many of these lesions will probably never progress to an invasive life-threatening cancer.[1]

What does all this mean? Is needle-directed biopsy overused? First, I heartily agree with the conclusions of Shields and associates that too many biopsies in their series were done for probably benign lesions seen at mammography in women younger than 50.[8] I also think that too many biopsies were done in their entire series (PPV 19%) and in many other published series.

Shields and colleagues also suggest that women younger than 50 who have nonpalpable breast lesions on their mammograms should have those examinations reviewed by an experienced mammographer before biopsy. Again, I fully agree with this recommendation, but it does not go far enough. Any woman who has a nonpalpable breast lesion recommended for biopsy should have that recommendation made, or confirmed, by an experienced mammographer.[3,7] Such consultations rarely require a formal written report and can be accomplished in a few minutes if the referring physician is in attendance. Our radiology department does about two such consultations per day at no charge. In my opinion, no surgeon or institution should perform biopsies of nonpalpable lesions without the available skills of dedicated mammographers.

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Treating Hansen's Disease in Developing Countries

To the Editor: The review[1] and editorial[2] on Hansen's disease in the June 1993 issue were most welcome, especially as few articles on this interesting and unique disease appear in standard US medical journals. In his review, Dr Gelber presents two different treatment programs. For multibacillary Hansen's disease, the World Health Organization (WHO) advocates multidrug, partially supervised therapy with the duration of therapy based on microbiologic examination; Dr Gelber recommends two drugs for three years followed by dapsone for life. While we tend to follow WHO protocols because of the well-written guides available describing this program,[3-5] an occasional stateside expert will drop in and promote the latter treatment. This tends to confuse patients and us. Given the success of multidrug therapy worldwide as described by Dr Miller in his editorial comments, what data are there to support Dr Gelber's recommendations?

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* * *

To the Editor: Dr Gelber's concise review on leprosy was very informative for primary care physicians in the current immigrant era. I would like to clarify certain epidemiologic and treatment aspects delineated by him and further elucidate the data on the Lucio's phenomenon.

In addition to anthrax mentioned by Dr Gelber, *Pseudomonas aeruginosa* was the other described human pathogen before Hansen's report in 1874.[1(p14)] Dr Gelber mentions bugs and mosquitoes as possible arthropod vectors in transmission of the disease. Other arthropods such as flies may also be capable of carrying leprosy bacilli from skin and nasal secretions.[2] Rees stresses the importance of controlling the fly population in and around leprosy units.[3] *Mycobacterium leprae* can remain viable in desiccated nasal secretions for one to seven days,[4] and transmission by flies may be a more plausible alternative in developing countries than inoculation by bacilli-laden soil through bare feet as proposed by Dr Gelber.

A notable omission in this review is the importance of poor housing and hygiene, which play a crucial part in the spread of leprosy.[5]

Dr Gelber cites high cost as the factor for which the World Health Organization (WHO) recommends once-a-month dosing of rifampicin [called rifampin in the United States] in the multibacillary treatment protocols for developing nations. A number of trials have shown that the rapid, highly potent bactericidal action of rifampicin renders human skin noninfective to mice in 5 to 14 days.[6,7] In fact, some protocols for multibacillary cases, such as the modified WHO regimen adopted by the Indian government in its National Leprosy Eradication Program, incorporate a daily dosing of rifampicin from day 1 to day 14 of therapy followed by the same recommendations as in the WHO regimen—the multiplication time for the lepra bacilli is around 14 days—with good success. Thus, the daily dosing of patients with rifampicin for as long as three years as suggested by Dr Gelber seems superfluous, exposing patients to adverse effects and enhancing the possibility of drug resistance.

The Lucio's phenomenon outlined by Dr Gelber is not exclusive to Mexico, as shown by Frenken in his translation of papers by Lucio and Latapi.[5] In fact, in many instances it mimics myxedema and may be misdiagnosed: In regions of the world where leprosy is endemic, a diagnosis of myxedema should never be made before examining the skin smears for leprosy bacilli.[1(p37)] Rea and Ridley distinguish Lucio's phenomenon from erythema nodosum leprosum by ischemic epidermal necrosis, necrotizing vasculitis of small blood vessels in upper dermis, several foci of endothelial proliferation of middermal vessels, and by the presence of a large number of bacilli in endothelial cells. In erythema nodosum leprosum, vasculitis does not play a primary role.[8]

With the increasing influx of immigrants, we are bound to see a drastic increase in the number of cases of Hansen's disease. Sufficient training must be incorporated into various residency training programs in the United States. As an international medical graduate from leprosy-endemic areas in India, I found my buried memories of this disabling disease being stirred by Dr Gelber's stark review.

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* * *

Dr Gelber Responds

To the Editor: I am gratified that my Medical Grand Rounds stimulated further insights. Because the interest has been focused on the differences between the therapy I and other US clinicians[1-3] use for multibacillary leprosy and that recommended by the World Health Organization (WHO),[4] further comments on this complex therapeutic decision appear to be in order. I recommend for my adult patients in the United States daily dapsone, 100 mg, and daily rifampin for three years, followed by daily dapsone, 100 mg, indefinitely. The WHO advocates daily dapsone, 100 mg, plus daily clofazimine, 50 mg, as well as monthly supervised rifampin, 600 mg, plus clofazimine, 300 mg. The WHO recommends that this treatment be administered for at least two years or until smears become negative (generally four to six years).

We do not generally recommend the use of clofazimine as part of our multidrug regimen for multibacillary leprosy. The inclusion of clofazimine in the WHO regimen was largely dictated by a concern with the high prevalence of primary dapsone resistance and the need for a reliable companion antimicrobial drug to be used in combination with rifampin. Because in a large series of multibacillary untreated patients[5] we did not detect any clinically relevant primary dapsone resistance in the United States, we find dapsone to be an acceptable companion to rifampin; clofazimine is therefore unnecessary. Furthermore, the skin discoloration resulting from clofazimine is cosmetically unacceptable to many of our lighter-skinned, particularly Asian, patients, marking them as "lepers."

Because *Mycobacterium leprae* cannot be grown in vitro and our rodent systems are sufficiently insensitive to monitor either directly or from human biopsies the relative killing of *M leprae* by daily versus monthly rifampin treatment, the preferred tempo of rifampin administration has been impossible to assess. Nonetheless, common sense would dictate that the killing of *M leprae* by daily therapy would at least be equivalent, and likely superior, to monthly administration. The WHO's decision to advocate monthly rifampin therapy is certainly based on its extraordinary bactericidal activity for *M leprae* and the prohibitive cost of daily rifampin for many developing countries where leprosy is a major public health problem. These financial considerations are not applicable to the developed world.

There is little doubt that noncompliance and low-dose therapy resulted in a high prevalence of secondary dapsone resistance in several locales,[6-8] and indeed suboptimal therapy in vitro is the classical means of isolating antimicrobial-resistant mutants. Thus, I would disagree with the assertion of Dr Vasireddi that daily rifampin therapy would be more dangerous than monthly rifampin in resulting in rifampin-resistant relapse. We have had considerable experience giving rifampin daily for the three years' duration we advocate without any additional toxicity than that encountered in the first few months. Most of the serious, life-threatening toxic effects of rifampin—thrombocytopenia, renal failure, and severe hemolytic anemia—are the result of intermittent therapy, in this respect once a month being fortunately implicated less than once a week. In a recent editorial review, Pattyn analyzed several different frequencies of rifampin administration used for multibacillary leprosy and found that equivalent amounts of rifampin given daily result in a lower relapse rate than intermittent administration, generally twice a week.[9]

Last is the issue of the relative efficacy of lifelong versus finite therapy for multibacillary leprosy. There has been an enormous experience with lifelong, mostly dapsone monotherapy, since the 1940s. Unless dapsone resistance developed, which it did only 2.5%[6] to 10%[10] of the time with dapsone monotherapy, the disease remained regularly arrested. Certainly the addition of rifampin daily for three years would reduce the *M leprae* population to a level where the presence of any viable dapsone-resistant *M leprae* would be exceedingly unlikely. Although our US experience is unpublished, personally I have treated more than 150 patients since 1979 in the manner outlined and have found in compliant patients absolutely no relapses. Although WHO multidrug therapy has cleared many patients from the leprosy rolls, it is not clear that long-term relapse rates will ultimately prove acceptably low. The evaluation of this issue is compounded by the fact that unlike short-course multidrug therapy for pulmonary tuberculosis, where relapses occur generally within six months after the completion of therapy, in multibacillary-leprosy patients treated with rifampin-containing regimens relapses largely occur only after five or more years.[9,11] For WHO's multidrug therapy for multibacillary leprosy, there is little experience with follow-up evaluation of this duration. Most recently, however, two-year multidrug therapy for multibacillary leprosy in one locale was found associated with a 10% relapse rate by five years,[9] which has been recently revised with additional follow-up to 20%. If this is to be the general experience with the WHO regimen, our recommendations for more prolonged therapy seem well justified.

Conflicting regimens can be confusing. Unfortunately, the data currently available leave room for valid alternative opinions, even among experts. Controlling leprosy in the developing world and treating patients in the United States may with reason be different. In the United States we may not be as severely constrained by finances. The important thing is not which formula is chosen but maintaining long-term compliance, drug supplies, and careful follow-up. Currently, less than half of the world's Hansen's disease patients receive any therapy at all. Of those, less than half receive anything other than dapsone alone. Whatever the regimen selected, the therapy for multibacillary leprosy requires multidrug regimens for a considerable time and a long follow-up.

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Specialty Care Needs of a Medically Indigent Adult Population

To the Editor: Proposed changes in the national health care system include health coverage for persons currently considered "medically indigent." This group includes the 37 million Americans completely uninsured and those currently covered by state and local government-funded programs such as the medically indigent adult county medical services (CMS) programs in California.[1] Although it is clear that a strong primary care network will need to be in place, the specialty care needs of these people will be substantial.[2]

San Diego County provides physical health services to approximately 22,000 medically indigent adults 21 to 65 years old. We recently reviewed the specialty care needs of these patients and compared them with the specialists available. In fiscal year 1992, 9,202 referrals were made to 328 specialists. The burden of specialty care fell to the greatest extent on ophthalmology (22% of referrals) and orthopedics (11%). General surgery (10%) and otolaryngology (8%) were also in high demand, followed by cardiology (8%), urology (7%), and neurology (7%).

The CMS program in San Diego experiences varying participation among specialties, with only 17% of county specialists accepting CMS patients. This maldistribution results in large referral-to-physician ratios (greater than 50 referrals per physician) falling on the dermatologists, endocrinologists, neurologists, and otolaryngologists. Uneven physician participation results in administrative resources being used to find physicians to care for these patients. The proposed reforms, however, would pay physicians equally for the formerly indigent and formerly insured patients. Assuming equal participation of physicians across specialties and current utilization patterns, the referral-to-physician ratio would be realigned. These recalculated ratios are highest in the fields of gastroenterology, neurology, ophthalmology, and otolaryngology; although orthopedics, surgery, cardiology, and urology would also be in high demand, the large number of these specialists countywide would result in much lower patient-physician ratios.

Eliminating economic barriers will not result in equal access to all specialists, because of geographic, language, and cultural barriers. It is, however, refreshing to consider that true health care reform could change the attitudes towards previously medically indigent adults from a burden and duty to a sought-after patient base, eliminating the time and money spent in seeking care for these patients.

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Improving Response to Domestic Violence

To the Editor: On reading Dr Patricia Salber's highly relevant epitome, "Improving Emergency Department Response to Victims of Domestic Violence," in the November 1993 issue,[1] a particular need in the care of these patients comes to mind. Working as a forensic pathologist in a coroner's office within shouting distance of the regional level I trauma center, I review emergency department records of injured patients who die. The injury assessments in these records may be adequate for treatment, but they are usually substandard for medicolegal purposes. I assume that this is also the case for many injured patients who survive and are therefore never evaluated by a forensic specialist.

In my experience, the training of emergency physicians generally is inadequate to prepare them for the task of accurately assessing injuries using proper forensic terms. Many do not appreciate the difference between a laceration and a cut, for instance. Emergency physicians often have a more pressing matter on their minds—saving the injured patient's life—and can spare little time for detailed wound evaluation and documentation. Nevertheless, injured patients should be given proper medicolegal evaluation. Inaccurate wound description can compromise treatment and may destroy the patient's right to compensation. Patients' need for justice on the criminal or civil level is as valid as their need for competent medical and surgical therapy.

Despite these farther-reaching needs, few centers in the United States have begun clinical forensic medicine training programs for residents and fellows in emergency medicine and other clinical specialties.[2] We are still far behind countries such as Great Britain, where a police surgeon—a clinician with specific forensic training and certification—is available. As a result, our quality of medicolegal evidence in cases with surviving victims, including victims of domestic violence of all sorts, is compromised.

Our forensic pathology group has offered to initiate such a program in our area, and the concept has been well received. So far, only the concept exists because funding, staffing, and other particulars are in limbo. I would encourage forensic pathologists and their clinical colleagues, along with attorneys and judges, seriously to consider the necessity of such programs in their communities. Until we establish a competent system of forensic medicine in this country, we will continue to underserve the needs of victims suffering from all forms of violence.

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Dr Salber Responds

To the Editor: Dr Reiber's letter raises an interesting point. As emergency physicians, trauma surgeons, and other physicians caring for injured patients are becoming increasingly aware of societal violence—including family violence—as a cause of injuries, the need for training in forensic evaluation is more apparent. Such evaluation would increase our ability to diagnose violence as the cause of an injury, thereby increasing the chances for a referral or intervention to break the cycle of violence. In addition, documentation of a forensic evaluation may help injured patients who seek protection or redress in the judicial system. The best treatment of victims of violence will require a team approach. I applaud Dr Reiber's suggestion that forensic pathologists should be added to the team.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

A Loss and a Lesson

BARRY L. ROTMAN, MD, *Palo Alto, California*

"Doctor, I need your signature on this death certificate."

"Oh? Whose death certificate?"

"John P."

"Ah, I see. Do you have any details regarding his death?"

"All I have is that he expired this morning at 10:20 AM. *They need his body as soon as possible. Could you sign the certificate now?"*

"Yeah. I'll be right over."

A brief, matter-of-fact exchange, one of hundreds that fill a physician's day. But this one was different. The hollow, bureaucratic communication of John P.'s death jarred me. The message reverberated within me, creating a slow, sinking feeling of sadness.

I had first met John P. a year earlier. He was an optimistic, rugged ex-military man with a stout build and an energetic countenance that belied his 75 years. A piecemeal collection of my experiences with John ran through my mind: my discussing the differential diagnosis of hemoptysis, his downplaying the importance of new back pain, then new hip pain, watching him walk weakly out of clinic, leaning heavily on the wall, refusing any assistance. When we last talked, he chastised me for notifying the Department of Motor Vehicles to revoke his driving license, adamantly asserting that he "felt fine"—despite high-dose narcotics and profound cachexia—and vowing to appeal the decision.

John would not openly acknowledge that he was dying of cancer. Our discussions, reviewing his studies and pathology reports, often ended with his making lighthearted remarks that denied his progressively declining condition. His favorite comment was, "Gee, Doc, you seem more concerned about this than I am." Initially I was frustrated with John. I felt certain that somehow he would suffer because of his refusal to accept his condition. As the months passed, he kept all of his radiation oncology appointments, sent me a form willing his body to the medical school, enrolled in the home hospice program, and then, despite never agreeing to a "No Code Blue" status, died quietly at home.

John reminded me of a simple adage from a psychiatry class in medical school—never take away a person's defense mechanisms unless you can replace them with something else. John's stoicism was an adaptive response. A fiercely independent man, his travels and character had left him alone, without close friends or family to care for him. In retrospect, I do not think he was harmed by his inability to accept his disease or his choice not to discuss it. Despite his denial, he took care of the necessary tasks, finding a temporary security in a nonsensical contradiction between his actions and his beliefs. He confronted death in his own manner and was able to preserve his character and dignity.

Walking out of the decedent affairs office, the weight of John's death pressed upon me, more so than many other patients' deaths. I was puzzled by my response. As an internist, had I not grown accustomed to death and loss?

My association with death began with the formaldehyde-scented anatomy of my first cadaver, an elderly woman whose body had been ravaged by metastatic pancreatic cancer. During medical school I learned how to deliver bad news and how to listen to the fears of the terminally ill. After graduation, I had a greater responsibility and a closer contact with death. During residency, I have eased the pain of the dying, watched patients die before my eyes, consoled family members, and even revived the dead during resuscitations. Yet I have never received any formal instruction in confronting death. Often I have felt isolated. Attempts to discuss death with my peers are hindered by a general reluctance to express fear or pain. Instead, I have developed my own approach, striving to balance the emotional openness necessary for compassion with enough reserve and distance to preserve my own psyche.

John P.'s death somehow caught me off guard, bypassing my own defense mechanisms and allowing me to experience the pain of his loss. In doing so, I realized the tremendous magnitude of the grief that I normally filter out. I, too, employ a form of denial.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Rotman BL: A loss and a lesson. West J Med 1994; 160:282)

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Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints, with the figure number, author's name, and top of the photo indicated with a label on the back. Patients (and relatives) have a right to anonymity in published clinical documentation. Details that might identify patients should be avoided unless essential for scientific purposes. Masking of the eye region in photographs of patients may be inadequate protection of anonymity. If identification of patients is unavoidable, informed consent should be obtained, and this should be clearly stated in the article. Changing data on patients should not be used as a way of securing anonymity. Figure legends, to be typed in sequence on the same page, should be in complete sentences. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

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All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.

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- Original manuscript and 2 copies
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THE DIVISION OF FAMILY MEDICINE AT THE UNIVERSITY OF CALIFORNIA, SAN DIEGO is seeking faculty members interested in combining clinical practice with clinical teaching. The positions will be at the Assistant Professor level, non-tenure track. The positions involve participating in a growing community-based, full spectrum Family Practice in a multicultural community with a full range of ages, socioeconomic, and health care payor systems. Opportunities for student and resident training are incorporated in the role. Candidates should be BC in Family Medicine with a strong commitment to teaching, clinical practice, and scholarship. Rank and salary, commensurate with qualifications and experience, based on UC scale. Interested candidates should send a CV and names of three references to:

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(Continued on Page 286)

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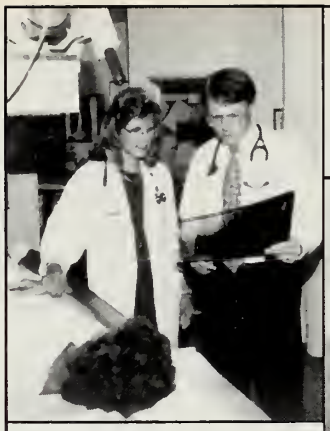

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(Continued from Page 285)

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PHYSICIANS. California Department of Corrections has positions available for Internal Medicine, Primary Care, General Practice, and Family Practice at the California Correctional Center at Susanville. For more information, contact Stephen O'Barr, (916) 257-2181, ext 1213. Or FAX your résumé to (916) 322-5864. EOE.

SAN FRANCISCO BAY AREA. Energetic, recently trained BC/BE Pediatrician needed for 18 physician satellite of Palo Alto Medical Clinic, a 160 physician multispecialty group with a national reputation for innovation and excellence. Broad practice in growing bay area community. Excellent location with convenient access to San Francisco and Stanford. Competitive compensation/benefits package. Early partnership. Please send CV to David Hooper, PAMC, Fremont Center, 39500 Liberty St, Fremont, CA 94538.

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BC/BE FAMILY PRACTITIONER–CALIFORNIA. TDH invites comparison with other private practice opportunities. We offer guaranteed income initially and exceptional earning potential. A growing area with new businesses, our patient population is now 105,000. Well equipped, 112-bed hospital. Located near Sequoia National Park, Tulare offers a desirable family environment, all amenities. Beautiful homes, close to office and hospital, are reasonably priced. Good schools, abundant recreation. California license required. No OB. Contact Tulare District Hospital Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (800) 468-2687.

SEATTLE, WASHINGTON/PORTLAND, OREGON: Two BC Family Practitioners for expanding practice in idyllic Washington community. Includes OB. Near water and mountains. Short drive to Portland. Income guarantee, benefits, partnership possible. Or, join single specialty Family Practice group in Seattle or Portland with OB optional. Karla, (800) 789-1190.

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(Continued on Page 287)

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INTERNIST–PACIFIC NORTHWEST. The Everett Clinic, a 100 plus physician multispecialty group, is seeking BC/BE Primary Care Internist to associate with 12 person department. Clinic is 25 miles north of Seattle and has four rapidly expanding satellite offices. Everett has two accredited hospitals with 217 and 257 beds. Opportunity for exceptional personal/professional lifestyle. Position offers competitive salary with excellent benefits. Position open until filled. Send CV to Al Fisk, MD, The Everett Clinic, 3901 Hoyt Ave, Everett, WA 98201.

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FAMILY PHYSICIAN–LEWISTON, IDAHO
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CALIFORNIA. Expanding, public hospital located in desert community one hour north of Los Angeles seeks full-time BC/BE Pediatrician for both hospital and clinic patients. Salary DOQ. Send CV by April, 1994 to Dr Alena Baquet-Simpson, Acting Medical Director, High Desert Hospital, 44900 N 60th St W, Lancaster, CA 93536, or call (805) 945-8303. EOE/AAP. Women, minorities, and persons with disabilities are encouraged to apply.

PART-TIME MEDICAL CONSULTANT CONTRACTS. Physicians needed to work under contract, on a part-time basis for the Social Security Administration's Disability Insurance Program. Involves review of medical evidence in disability claims at 75 Hawthorne Street, San Francisco. No patient contact. Applicants must (1) have a valid license to practice medicine in the USA; (2) have current or recent clinical experience; and (3) be available between 6:30 AM and 5:30 PM Monday through Friday for case review. Subject to change, the specialties needed are Internal Medicine, Pediatrics, Neurology, Orthopedics/Physiatry, Psychiatry, and Psychology. The expected date of contract is 10-1-94. Women and minorities are encouraged to apply. If interested in receiving further information, submit written request by April 5, 1994 to Contracting Officer, 50 United Nations Plaza, Rm 403, San Francisco, CA 94102.

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GOOD NEWS!! New legislation allows for Safety Retirement Package. Call for additional information.

Contact: **Anne Perez** (916) 327-7081. Send or fax CV to:

California Department of Corrections
Dept. DHCS, P.O. Box 942883, Sacramento, CA 94283-0001.
Fax (916) 322-5864 EOE.

(Continued from Page 287)

PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call (800) 873-0786.**

EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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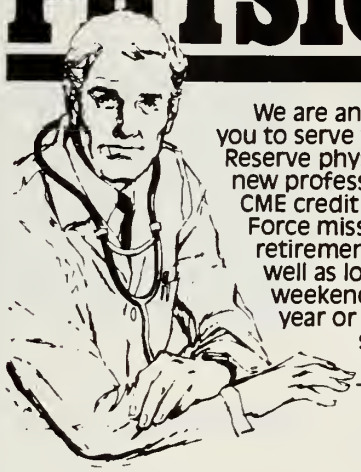

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Zantac® 150 (ranitidine hydrochloride) Tablets **BRIEF SUMMARY**
Zantac® 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in: 1. Short-term treatment of active duodenal ulcer. 2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers. 3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis). 4. Short-term treatment of active, benign gastric ulcer. 5. Treatment of gastroesophageal reflux disease (GERD). 6. Treatment of endoscopically diagnosed erosive esophagitis.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, GERD, and erosive esophagitis.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug or any of the ingredients.

PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy. 2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver. 3. Rare reports suggest that Zantac may precipitate acute porphyric attacks in patients with acute porphyria. Zantac should therefore be avoided in patients with a history of acute porphyria.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution). Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day. Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays. In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks.

Pregnancy: *Teratogenic Effects. Pregnancy Category B*: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias and myalgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported. When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed. Studies in dogs receiving dosages of Zantac® in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)

Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.

June 1993
RL-024
2165A

Zantac® 150 Tablets/Zantac® 300 Tablets: Glaxo Pharmaceuticals, Research Triangle Park, NC 27709. Zantac® Syrup: Manufactured for Glaxo Pharmaceuticals, Research Triangle Park, NC 27709, by Roxane Laboratories, Inc., Columbus, OH 43216.

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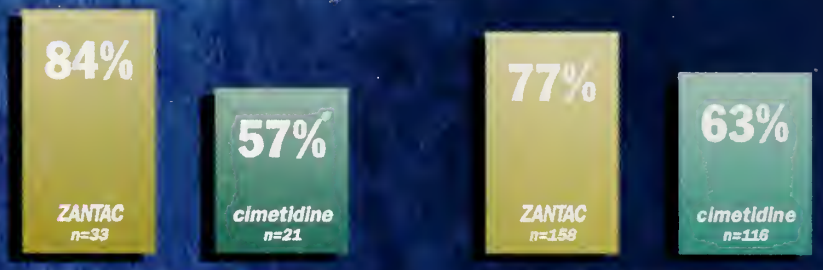
For Efficacy As Maintenance Therapy In Healed Duodenal Ulcer Disease

PROVEN SUPERIORITY

ZANTAC 150 mg h.s. superior to cimetidine 400 mg h.s. for maintenance therapy of healed duodenal ulcer disease at 1 year.[1,2]



P=0.01. Adapted from Silvis et al.[1*†]

P=0.004. Adapted from Gough et al.[2*]

*These trials used the currently recommended dosing regimens of ZANTAC (150 mg h.s.) and cimetidine (400 mg h.s.). A comparison of other dosing regimens has not been studied. The studied dosing regimens are not equivalent with respect to the degree and duration of acid suppression or suppression of nocturnal acid. The superiority of ZANTAC over cimetidine in these trials indicates that the dosing regimen currently recommended for cimetidine is less likely to be as successful in maintenance therapy.

†Percent estimates are determined by life-table estimates. If crude-rate estimates were used, percentage of patients ulcer free after 1 year would be 88% for ZANTAC and 71% for cimetidine. All patients were permitted p.r.n. antacids for relief of pain.

The safety profile of ZANTAC is confirmed in over 13 years of use and over 190 million patient treatments worldwide.† Low incidence of side effects. Headache, sometimes severe, was most frequently reported in controlled clinical trials, with an incidence rate not significantly different from placebo.[3]

†Estimate, Glaxo Inc.

In DU Maintenance Therapy

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets hs

Please see references and brief summary of Prescribing Information on adjacent page.

CERENEX™ PHARMACEUTICALS DIVISION OF GLAXO INC.

Glaxo/Roche Research Triangle Park, NC 27709

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Discover The Elegance Of A Hybrid

At first glance, it's the beauty of the hybrid Lily that catches the eye. The vibrant color. The delicately shaped petals. But study it more closely, and its *elegance* becomes apparent–a gentle blend of softness and strength.

At first glance, it's the enhanced performance of Vaseretic® that catches the eye. But study Vaseretic® more closely, and its *elegance* becomes apparent. The way its one-tablet, once-a-day dosage minimizes multiple medications. Minimizes the number of insurance copayments. And minimizes potassium supplementation.

A hybrid blending of tolerability and power that's available for the right patient. Vaseretic® is indicated for the treatment of hypertension in patients for whom combination therapy is appropriate.

And an elegant discovery for your practice.

VASERETIC® 10-25 *Next*

Enalapril Maleate-Hydrochlorothiazide

Vaseretic® is contraindicated in patients who are hypersensitive to any component of this product or to other sulfonamide–derived drugs and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.
Dosage must be individualized; the fixed combination is not for initial therapy.
Evaluation of the hypertensive patient should always include assessment of renal function.
For a Brief Summary of Prescribing Information, see adjacent pages.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General; Enalapril Maleate; Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions*, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy, Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*, below.)

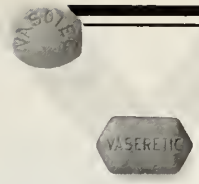
Enalapril Maleate; Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

10 mg



25 mg

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide; Teratogenic Effects. Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General; Enalapril Maleate, Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions.*)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients; Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension. Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions; Enalapril Maleate, Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution

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assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse bone marrow assay.

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy: Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*

Clinical Laboratory Test Findings: Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide—*Body as a Whole:* Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg

For more detailed information, consult your DuPont Pharma Representative or see Prescribing Information.

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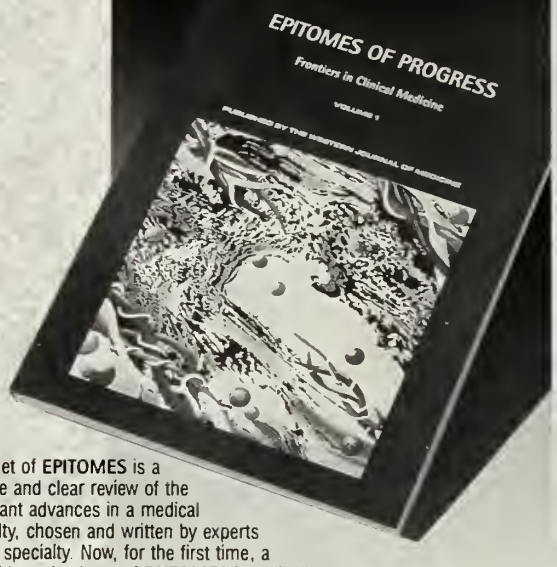
i-'pit-ə-mē\ *n* [L, fr. Gk *epitomē*, fr. *epitemnein* to cut short, fr. *epi-* + *temnein* to cut — more at TOME] (1520) **1 a :** a summary of a written work **b :** a brief presentation or statement of something **2 :** a typical or ideal example: EMBODIMENT (the British monarchy itself is the ~ of tradition —Richard Joseph) **3 :** Plural — *Epit-o-mes* — A regular FEATURE of *The Western Journal of Medicine*, now available in a single, bound volume.



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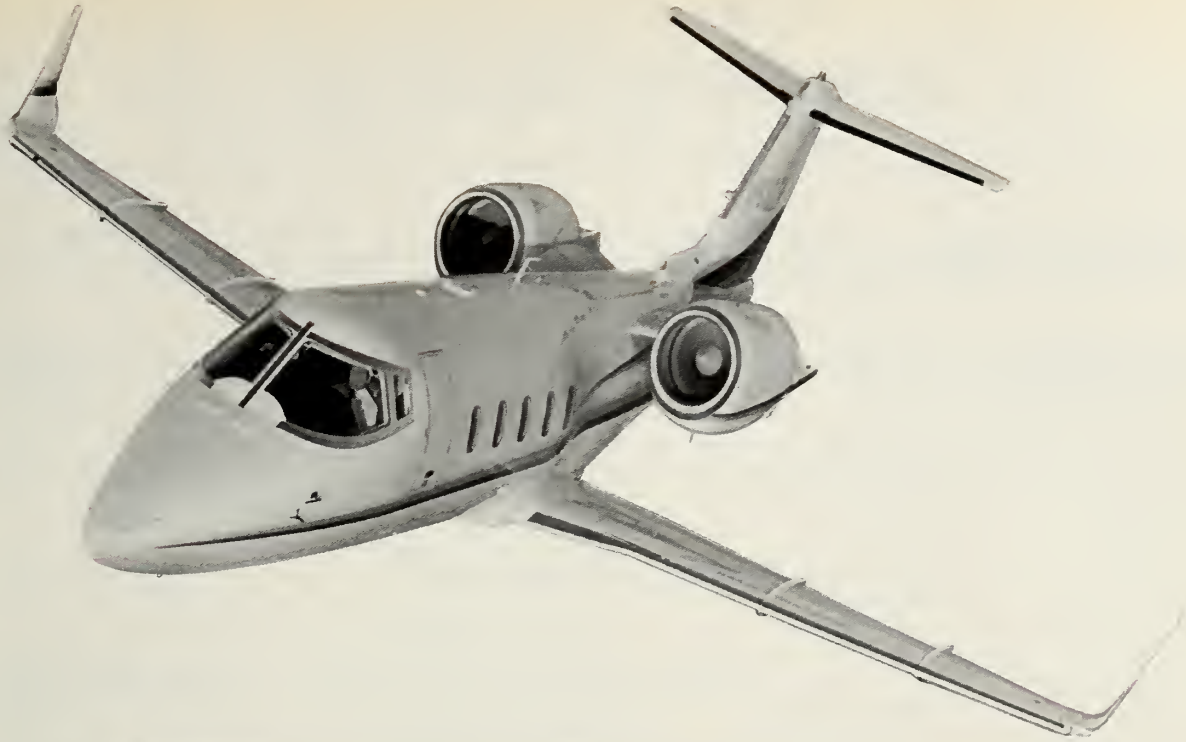

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

April 15-17—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Camelback Inn, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

April 21-22—**Advanced Pediatric Life Support: Provider Course.** Maricopa Medical Center, Phoenix. Thurs-Fri. Contact: (602) 267-5414.

April 22—**Pediatrics–Spring Symposium.** University of Arizona College of Medicine at Arizona Health Sciences Center, Tucson. Fri. Contact: Lynn Mascarella, U of A.

April 29-30—**Twenty-sixth Annual Pediatric Orthopedic Symposium.** Maricopa Medical Center. Fri-Sat. Contact: Beverly Anderson, (602) 267-5366.

May 4-6—**Practice Parameters and Guidelines: Impact on Quality.** American Board of Quality Assurance and Utilization Review Physicians at the Arizona Biltmore, Phoenix. Wed-Fri. Contact: (813) 286-4411.

May 5-6—**Advanced Cardiac Life Support: Provider Course.** Maricopa Medical Center, Phoenix. Thurs-Fri. Contact: (602) 267-5414.

May 13—**Pediatric Advanced Life Support: Recertification Course.** Phoenix Children's Hospital at Good Samaritan Regional Medical Center. Fri. Contact: (602) 239-3563.

May 14—**Topics in Head and Neck Reconstruction.** Mayo Clinic-Scottsdale at the Ashton B. Taylor Auditorium, Scottsdale. Sat. Contact: Tamara Zelinski, (602) 301-7447.

May 14-17—**1994 Annual Meeting—American Pediatric Surgical Association.** Loews Vantana Canyon Resort, Tucson. Sat-Mon. Contact: (816) 234-3579.

May 16-17—**Advanced Pediatric Life Support: Provider Course.** Maricopa Medical Center, Phoenix. Thurs-Fri. Contact: (602) 267-5414.

May 21—**Current Topics in Head and Neck Reconstruction.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Scottsdale. Sat. Contact: Tamara Zelinski, (602) 301-7447.

June 2-4—**Arizona Medical Association Annual Meeting**. Scottsdale Plaza Resort. Thurs-Sat. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.
Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.
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ANESTHESIOLOGY

May 19-22—**California Society of Anesthesiologists Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $225-$325. Contact: CSA. 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

May 22-27—**Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun-Fri. 45 hrs. $500. Contact: UCSD.

CARDIOLOGY

May 13-15—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Doubletree Resort, Palm Springs. Fri-Sun. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 3-5—**Pediatric Electrophysiology, Pacing Course, and Board Review.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. $425. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

July 22-24—**Coronary Heart Disease.** American College of Emergency Physicians at Marriott Tenaya, Yosemite. Fri-Sun. 11 hrs. Contact: Karen DeBont, Meetings Coordinator, 1500 W Canal Ct, Ste #500, Littleton, CO 80120-4528. (800) 421-3756.

July 24-28—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 19 hrs. Contact: UCD.

September 23-24—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Desert Inn, Las Vegas, NV. Fri-Sat. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

DERMATOLOGY

July 19-23—**11th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD and Scripps Clinic at La Jolla. Tues-Sat. 33 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037 (619) 554-8556.

August 8-10—**Dermatology for the Non-Dermatologists.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

April 26-27—**5th Annual High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at Pan Pacific Hotel, San Francisco. Tues-Wed. 15 hrs. $450-$495. Contact: Alpen Travel and Meeting, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 451-RISK (7475).

May 9-13—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 17-20—**BLS Instructor Course.** CPR Seminars at San Leandro. Fri-Mon. $100. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

June 20-24—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 21-22—**5th Annual High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at Pan Pacific Hotel, San Francisco. Tues-Wed. 15 hrs. $450-$495. Contact: Alpen Travel and Meeting, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 451-RISK (7475).

July 19-20—**5th Annual High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at Pan Pacific Hotel, San Francisco. Tues-Wed. 15 hrs. $450-$495. Contact: Alpen Travel and Meeting, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 451-RISK (7475).

July 29—**ACLS Recertification.** CPR Seminars at San Francisco. Fri. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

August 15-19—**Emergency Medicine Symposium II.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

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CONTINUING MEDICAL EDUCATION

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September 16—**Advanced Burn Life Support Course.** Torrance Memorial Burn Center at Torrance Memorial Hospital. Fri. 9 hrs. $220. Contact: Nancy Wise, (310) 517-4605.

September 17—**ACLS Recertification.** CPR Seminars at San Francisco. Fri. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

FAMILY PRACTICE/PRIMARY CARE

April 21-24—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

May 5-7—**Primary Care for the '90s.** University of Nevada School of Medicine at Resort at Squaw Creek, Olympic Valley. Thurs-Sat. 15.5 hrs. $260-$290. Contact: University of Nevada, Manville Bldg/342, Reno, NV 89557. (702) 784-4605.

May 11-14—**16th Semi-Annual Wound Management for Primary Care Health Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $250-$475. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

May 13-14—**Coming of Age: Geriatrics for Primary Care Providers–Part 1.** UCD at Sacramento. Fri-Sat. Contact: UCD.

May 31-June 4—**21st Annual UCLA Family Practice Refresher Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Tues-Sat. 32 hrs. $485. Contact: UCLA.

June 12-17—**18th Annual Fingers to the Toes Orthopaedics for Primary Care.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. 25 hrs. Contact: UCD.

June 23-26—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 18 hrs. $370. Contact: UCLA.

July 5-7—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Tues-Thurs. 20 hrs. $350. Contact: UCSF.

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JUNE, 1994

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June 13-14, 1994
NEWPORT BEACH, CALIFORNIA

UCI Family Practice Refresher Course
June 13-17, 1994
NEWPORT BEACH, CALIFORNIA

JULY, 1994

12th Annual Controversies in OB/GYN
July 6-9, 1994
MAUNA KEA RESORT, HAWAII

AUGUST, 1994

Fetal Heart Rate Monitoring
August 4-6, 1994
CENTURY CITY, CALIFORNIA

3rd Internal Medicine Board Review
August 8-12, 1994
NEWPORT BEACH, CALIFORNIA

SEPTEMBER, 1994

2nd International Symposium on the Difficult Airway
September 16-18, 1994
NEWPORT BEACH, CALIFORNIA

7th Annual Advanced OB/GYN & Transvaginal Ultrasound
September 29, 1994-October 1, 1994
ORANGE, CALIFORNIA

OCTOBER, 1994

Primary Care—1994
October 11-14, 1994
LANAI, HAWAII

Pediatrics for the Practitioner
October 17-20, 1994
ISLAND OF HAWAII

Update Clinical Medicine
October 17-20, 1994
ISLANO OF HAWAII

NOVEMBER, 1994

5th Annual Practical Methods in Diabetes Management
November 11-12, 1994
COSTA MESA, CALIFORNIA

Current Issues in Perinatal Medicine
November 11-13, 1994
RANCHO MIRAGE, CALIFORNIA

17th Annual OB/GYN Review Course
November 14-19, 1994
COSTA MESA, CALIFORNIA

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PROGRAM PROFILE

University Plastic Surgeons/ Center For Reconstructive Surgery

A 27-year-old who sustained a gunshot wound to the base of his thumb was left with (a) a composite defect including lost skin, muscle, tendon, nerve and bone; (b) simultaneous reconstruction of all these missing structures was successfully performed using a tissue flap from his opposite upper arm employing microsurgical techniques.

Microvascular reconstruction has dramatically expanded the field of plastic surgery, opening doors for subspecialists who perform radical resections for the ablation of tumors or who attempt salvage of extremities that have been severely traumatized.

The Reconstructive Surgery Team works closely with specialists in otolaryngology-head and neck surgery, neurosurgery, general surgery, orthopaedics, urology, oncology and rehabilitation. Together they incorporate a variety of procedures, blending innovative techniques that offer the greatest advantage for functional and aesthetic restoration, including:

Hand Surgery

Reconstructive hand surgery is a multifaceted discipline that incorporates techniques employed in several specialties: the treatment of bony injuries, the care of nerves and soft tissue, the restoration of mechanics — joints, tendons, and ligaments. Surgical specialists perform microsurgical replantation and reconstruction of complex hand injuries, and treat congenital hand deformities and hand burns.

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Reconstructive Microsurgery and Complex Wound Management

USC surgeons perform microsurgical free tissue transfer (using vascularized tissue flaps) to manage complex wounds which entails re-establishing circulation of the supplying arteries and draining veins between donor tissue and injury site.

Burn Reconstruction

Specialists in the secondary reconstruction of burn injuries use unique methods of restoring form and function. Surgeons have developed an operation that restores normal neck contour, and another that reconstructs ears, using materials which behave like living tissue. In facial reconstruction, they work to restore balance to the patient's features, focusing not only on skin coverage but also on the structure of the facial skeleton to compensate for the loss of soft tissue and scar contracture.

Treatment of Craniofacial Deformities

The oromandibular region is particularly complex. Through advances in techniques and instrumentation, reconstructive surgeons can move the forehead, change the position of the eyes, realign the jaws and reshape the underlying structure to make dramatic differences in craniofacial deformities.

UNIVERSITY PLASTIC SURGEONS

B. Chandrasekhar, M.D.
Bill Dougherty, M.D.
Susan E. Downey, M.D.
John Gross, M.D.
Larry S. Nichter, M.D.
John F. Reinisch, M.D.
Randolph Sherman, M.D.
Gerald M. Sloan, M.D.
Tad Wellisz, M.D.

Reconstructive Breast Surgery

One alternative, the TRAM flap breast reconstruction procedure, involves the use of abdominal skin and muscles to form a new breast. Other options include autologous tissue replacement, implants, and tissue expanders followed by breast implant.

Post-Cancer Reconstruction

Patients who require extensive disfiguring tumor resection are benefitted by advances in microvascular techniques and osseointegrated implants for facial prosthetic reconstruction. In addition, musculoskeletal tumors in the upper and lower extremities that once required amputation may be treated through limb salvage procedures that incorporate antibiotic therapy, tumor resection, immediate implantation of bone allograft or endoprostheses, and microvascular coverage using free tissue transfer.

Close Communication With Referring Physicians

Members of the University Plastic Surgeons/ Center for Reconstructive Surgery are committed to maintaining close contact with referring physicians to ensure effective patient management for optimal recovery.

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August 5-7—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 19-21—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 19-21—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien, San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

April 30—**Caring for the Older Female Patient.** UCSF and Mount Zion Center on Aging at Miyako Hotel, San Francisco. Sat. Contact: Mount Zion Institute on Aging, (415) 750-4170.

May 13-14—**Coming of Age: Geriatrics for the Primary Care Provider—Part I.** UCD at Sacramento Inn. Fri-Sat. 13 hrs. Contact: UCD.

May 14—**Geriatric Medicine.** Sutter Community Hospital at Fairfield. Sat. Contact: Sutter Hospital, 2800 L St, Sacramento 95815. (800) 777-0231.

June 4—**Heart Disease in the Elderly.** UCSF and Mount Zion Center on Aging at Miyako Hotel, San Francisco. Sat. Contact: Mount Zion Institute on Aging, (415) 750-4170.

1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

INFECTIOUS DISEASE

May 11-13—**Advances in Infectious Diseases.** UCSF at Ana Hotel, San Francisco. Wed-Fri. 16.5 hrs. $410. Contact: UCSF.

June 3—**8th Annual AIDS Conference.** Alta Bates Medical Center at Parc Oakland Hotel. Fri. 7 hrs. Contact: Caroline Carey, Medical Education. (510) 204-3884.

INTERNAL MEDICINE

May 20-22—**California Society of Internal Medicine Annual Meeting** at Hyatt Newporter Hotel, Newport Beach. Fri-Sun. 8 hrs. $100-$175. Contact: CSIM, PO Box 880606, San Francisco 94188-0606. (415) 882-5198.

May 23-27—**Advances in Internal Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 33 hrs. $630. Contact: UCSF.

June 4—**Pain Management.** Sutter Community Hospital at Jackson. Sat. Contact: Sutter Community, 2800 L St, Sacramento 95816. (800) 777-0231.

June 17-19—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. 12 hrs. Contact: Karen Debont, 1500 W Canal Crt, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 20-24—**Advances in Internal Medicine.** UCSF at Cole Hall, UCSF Campus. Mon-Fri. 33 hrs. Contact: UCSF.

July 9-16—**3rd National Kaiser Permanente Internal Medicine Conference.** Permanente Medical Group at Ritz-Carlton Hotel, Kapalua, Maui, Hawaii. 1 wk. 22 hrs. Contact: Eric Tepper, MD, 3400 Delta Fair Blvd, Antioch 94509. (510) 779-5211.

August 14-19—**11th Annual New Advances in Internal Medicine.** UCD at Hyatt Monterey. Sun-Fri. Contact: UCD.

August 26-September 1—**Comprehensive Nephrology Review Course.** UCLA School of Medicine at Beverly Hilton Hotel, Beverly Hills. Fri-Thurs. 51 hrs. $895. Contact: UCLA.

September 17-19—**1994 International Symposium on Bone Marrow Transplantation.** Sutter Community Hospital at Fairmont Hotel, San Francisco. Sat-Mon. Contact: Sutter Community, 2800 L St, Sacramento 95816. (800) 777-0231.

OB/GYN

April 20-24—**Pacific Coast Fertility Society Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 17 hrs. Contact: Director, Continuing Medical Education, 15731 Imperial Hwy, Ste 427, La Mirada 90638-2510. (310) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

June 3-4—**Occupational and Environmental Medicine.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

July 25-29—**8th Annual Sports Medicine.** UCSD at San Diego Princess Resort. Mon-Fri. 20 hrs. $395. Contact: UCSD.

ONCOLOGY

April 30—**Cancer in Women: Management of Breast and Gynecologic Malignancies.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

June 18—**Cancer.** Sutter Community Hospital at Sacramento. Sat. Contact: Sutter Community, 2800 L St, Sacramento 95816. (800) 777-0231.

July 19-22—**Pan Pacific Lymphoma Conference.** University of Nebraska Medical Center at Ritz-Carlton-Mauna Lani, Kohala Coast, Hawaii. Tues-Fri. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

OPHTHALMOLOGY

May 21—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

ORTHOPEDICS

May 19-21—**Fractures of the Shoulder and Elbow.** American Academy of Orthopaedic Surgeons at San Diego Marriott Hotel and Marina. Thurs-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

May 20-21—**New Techniques and Technologies in Total Hip Replacement.** American Academy of Orthopaedic Surgeons at Sheraton Palace Hotel, San Francisco. Fri-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs. (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

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CONTINUING MEDICAL EDUCATION

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July 8-9—**Spine and Strength Symposium.** UCSD at Marriott, La Jolla. Fri-Sat. $300. Contact: Kerri Kazala, 4150 Regents Park Row #300, La Jolla 92037. (619) 625-0026.

July 15-16—**Hand Review 1994.** UCD at Holiday Inn, Capitol Plaza, Sacramento. Fri-Sat. $275. Contact: UCD.

August 13-17—**58th Annual Meeting Western Orthopedic Association at Long Beach.** Sat-Wed. 18 hrs. Contact: H. J. Martin, (510) 671-2164.

1994—**Educational Program for Musculoskeletal Evaluation and Rehabilitation.** UCSD at La Jolla. 35.5 hrs. $500. Contact: UCSD.

OTOLARYNGOLOGY

May 15-20 & June 5-10—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

PATHOLOGY

April 16—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Fri. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

April 29—**3rd Annual Pathology Forum.** UCD at Cancer Center Auditorium. Fri. 7 hrs. $95. Contact: UCD.

May 26-28—**10th Annual Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

September 17-21—**9th Combined Skin Pathology Course and 5th Annual Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sat-Wed. 40 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

April 15-16—**Pediatric Dermatology for the Practitioner.** Children's Hospital and Health Center at L'Auberge Del Mar Hotel, San Diego. Fri-Sat. 12 hrs. $245. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

May 12-14—**27th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

June 1-3—**13th Annual Child Abuse and Neglect Conference.** UCD at Radisson Hotel, Sacramento. Wed-Fri. Contact: UCD.

June 3-5—**Pediatric Electrophysiology, Pacing Course and Board Review.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. $425. Contact: Children's Hospital, 30202 Children's Way, San Diego 92123. (619) 576-4072.

June 24-26—**Current Concepts in Child Neurology 1994.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15 hrs. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

July 15-17—**2nd Annual Pediatric Update.** Stanford University School of Medicine at Lucile Packard Children's Hospital, Palo Alto. Fri-Sun. Contact: Elinor Meyer, Medical Outreach Dept, 725 Welch Rd, Palo Alto 94304. (415) 497-8554.

August 22-24—**Pediatrics Update 1994.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

April 22-26—**The Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Colonial Inn, La Jolla. Fri-Tues. 26 hrs. $550. Contact: UCSD.

April 30-May 1—**Self Psychological Revolution: Psychotherapy Since Kohut.** UCSD at Pan Pacific Hotel, San Diego. Sat-Sun. 13 hrs. $325. Contact: UCSD.

June 28-July 3—**Neuropsychiatric Aspects of Aging: Update and Review.** Southern California Neuropsychiatric Institute at Mauna Kea Hotel, Hawaii. Tues-Sun. 22 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

1994—**Basic Clinical Hypnosis Training.** UCSD at La Jolla. Ongoing. 30 hrs. $245. Contact: UCSD.

PULMONARY MEDICINE

June 5—**Pleuropulmonary Neoplasms.** California Tumor Tissue Registry at Westin South Coast Plaza, Costa Mesa. Sun. 8 hrs. Contact: Anne Chism, Loma Linda University, Department of Pathology, 11021 Campus Ave, AH 335, Loma Linda 92354. (909) 824-4788.

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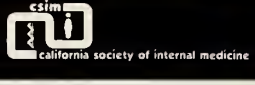

8th Annual Low Back Pain Conference

June 17-19, 1994 ~ Bally's, Las Vegas

The Low Back Pain Conference offers the physician the opportunity to learn how better to diagnose and treat low back pain. You will be exposed to the broad spectrum of both causes and treatments. The Conference uses a multi-disciplinary approach with all the necessary clinicians in one location and is one of the most comprehensive meetings held on the subject.

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The Western Journal of Medicine

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MARKO R. GUDZIAK, MD, and ANTHONY Y. SMITH, MD

From the Department of Surgery, Division of Urology, University of New Mexico School of Medicine, Albuquerque.

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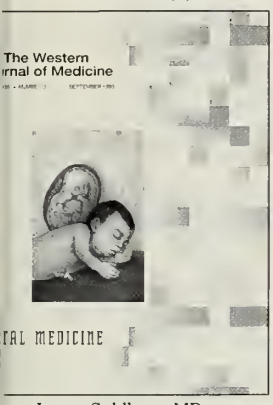
SPECIAL ISSUES

THE WESTERN JOURNAL OF MEDICINE

FETAL MEDICINE

SEPTEMBER 1993



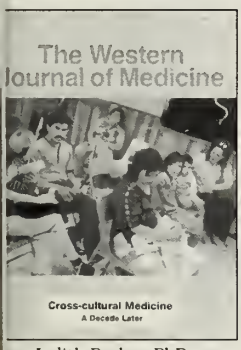
James Goldberg, MD
Special Issue Editor, 1993

Articles Include:

- CLINICAL TERATOLOGY—AN EXPANDING AREA IN PREVENTIVE ANTENATAL CARE
- CARDIAC ULTRASOUND IN STRUCTURAL ABNORMALITIES AND ARRHYTHMIAS—RECOGNITION AND TREATMENT
- ETHICS OF FETAL TISSUE TRANSPLANTATION
- AMNIOCENTESIS AND CHORIONIC VILLUS SAMPLING
- PRENATAL DIAGNOSIS USING FETAL CELLS FROM THE MATERNAL CIRCULATION
- FETAL PHARMACOLOGIC THERAPY
- ETHICAL CONSIDERATIONS IN PRENATAL DIAGNOSIS
- MATERNAL SERUM SCREENING FOR NEURAL TUBE DEFECTS AND FETAL CHROMOSOME ABNORMALITIES
- FETAL ULTRASOUND
- DIAGNOSIS AND SIGNIFICANCE OF FETAL INFECTION
- STEM CELL TRANSPLANTATION
- FETAL TISSUE SAMPLING
- SCARLESS SKIN WOUND REPAIR IN THE FETUS
- ETHICAL ISSUES IN OFFERING AND RECOMMENDING FETAL THERAPY
- INTRAUTERINE TRANSFUSION—RED CELLS AND PLATELETS

AND MANY MORE

Cross-cultural Medicine—A Decade Later



Judith Barker, PhD
Speciol Issue Editor, 1992

Ethnic Groups Covered:

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Cross-cultural Medicine

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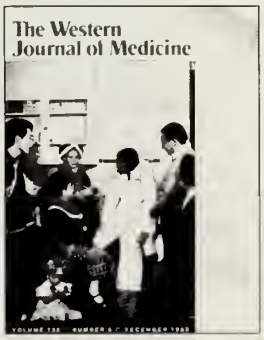

M. Margaret Clark, PhD
Special Issue Editor, 1983

Ethnic Groups Covered:

PHILIPPINO, AFRICAN-AMERICAN, JAPANESE, SOUTHEAST ASIAN, JAMAICAN, PACIFIC ISLANDER, CHINESE, LATINO, SOVIET JEWS, NATIVE ALASKAN, AND MIDDLE EASTERN.

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APRIL 7-10 1994

FOCUS ON THE FEMALE PATIENT
LOCATION: Howey-in-the-Hills (Orlando), Florida
SPECIALTY: Primary Care, Ob/Gyn
CME CREDIT: AMA Category I, 16 hours
FEE: SMA Member $310; Nonmember $435

APRIL 15-17, 1994

ADDICTION MEDICINE
LOCATION: New Orleans, Louisiana
SPECIALTY: Primary Care, Psychiatry, Emergency Medicine
CME CREDIT: AMA Category I, 15 hours
FEE: SMA Member $350; Nonmember $475

APRIL 15-17, 1994

ORTHOPAEDIC UPDATE
LOCATION: Wrightsville Beach, NC
SPECIALTY: Orthopaedic Surgery
CME CREDIT: AMA Category I, 14 hours
FEE: SOA Member $125; SMA Member $225; Nonmember $350

APRIL 22-24, 1994

INFECTIOUS DISEASES
LOCATION: Atlanta, Georgia
SPECIALTY: Primary Care
CME CREDIT: AMA Category I, 15 hours
FEE: SMA Member $310; Nonmember $435

MAY 20-22, 1994

CURRENT CONCEPTS IN ORTHOPAEDICS
LOCATION: Baltimore, Maryland
SPECIALTY: Orthopaedic Surgery
CME CREDIT: AMA Category I
FEE: SOA Member $175; SMA Member $275; Nonmember $400; Resident or Fellow $50; Nonphysician $75

JUNE 9-11, 1994

SOUTHERN ASSOCIATION FOR GERIATRIC MEDICINE, FOURTH ANNUAL MEETING
LOCATION: Hilton Head, South Carolina
SPECIALTY: Geriatrics
CME CREDIT: AMA Category I
FEE: To be announced

JUNE 12-16, 1994

EIGHTEENTH SYMPOSIUM ON LUNG DISEASE
LOCATION: Sea Island, Georgia
SPECIALTY: Pulmonary and Critical Care Medicine
CME CREDIT: AMA Category I, 22 hours
FEE: SMA/Southern ACCP Member $415; Nonmember $540; Nonphysician $275

JUNE 16-18, 1994

MUSCULOSKELETAL IMAGING
LOCATION: Nevis, Caribbean
SPECIALTY: Radiology
CME CREDIT: AMA Category I, 17 hours
FEE: SMA Member $395; Nonmember $520; Nonphysician $275

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!

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EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Dermatology

Items of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

360 **Nevi—An Update**
RONALD J. BARR, MD

360 **Look Out for Latex**
GARY W. COLE, MD

361 **Acyclovir to Treat Varicella**
ILONA J. FRIEDEN, MD

362 **Polymerase Chain Reaction in Dermatology**
ROBERT W. GOLTZ, MD

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HUBERT T. GREENWAY, MD

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From the Medical Service and Psychology Service, Department of Veterans Affairs Medical Center, and the Departments of Medicine, Psychiatry, and Medical Psychology, Oregon Health Sciences University School of Medicine, Portland.

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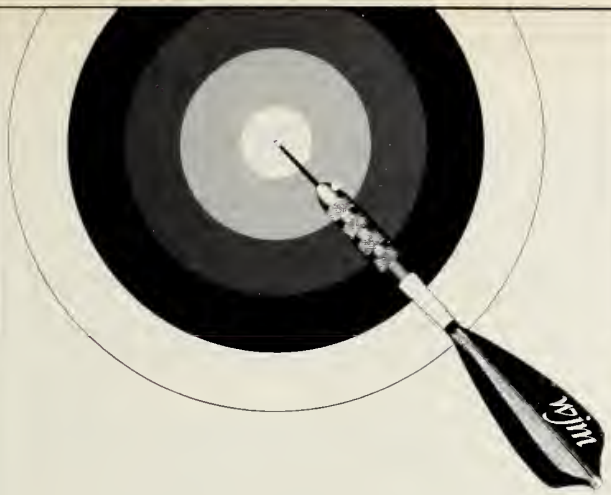

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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August 12-14—**Diagnosis and Management of Respiratory Diseases.** American College of Emergency Physicians at Hyatt Regency, Lake Tahoe, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

September 23-25—**Diagnosis and Management of Respiratory Diseases.** American College of Emergency Physicians at Esmeralda Resort, Palm Springs. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

RADIOLOGY

April 17-22—**Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: UCSD.

May 22-25—**Advanced Echocardiography and Doppler Ultrasound.** American College of Cardiology at Hyatt Islandia, San Diego. Sun-Wed. 23 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

August 25-28—**Physics of Diagnostic Radiology.** UCD on Campus. Thurs-Sun. Contact: UCD.

1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

1994—**Visiting Fellowship Program of Endovaginal Sonography: Focus on Techniques and Application.** UCSD Medical Center. Monthly. 30 hrs. $600. Contact: UCSD.

SURGERY

June 23-25—**20th Annual Meeting of the Western Thoracic Surgical Association.** WTSA at Resort at Squaw Creek, Olympic Valley. Thurs-Sat. Contact: WTSA. (508) 526-8330.

GENERAL/MULTIDISCIPLINARY

May 21—**Risk Management.** Sutter Community Hospital at Sacramento. Sat. Contact: Sutter Hospital, 2800 L St, Sacramento 95816. (800) 777-0231.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

April 16—**Born Too Soon: Perinatal Conference.** P/SL Swedish Healthcare System at Presbyterian/St Luke's Medical Center, Denver. Sat. Contact: Mary Fletcher, (800) 633-6824.

June 12-18—**40th Annual Family Practice Review.** University of Colorado Health Sciences Center at YMCA of the Rockies, Estes Park. Sun-Sat. Contact: U of Colo.

July 8-10—**Common Problems in Primary Care.** P/SL Swedish Healthcare System at Snowmass. Fri-Sun. Contact: Nancy Manuel, (303) 788-6209.

July 8-10—**Current Concepts in Heart Failure: Medical Treatment to Mechanical Support and Transplantation.** P/SL Swedish Healthcare System at Snowmass. Fri-Sun. Contact: Nancy Manuel, (303) 788-6209 or P/SL CME Office, (800) 633-6824.

August 1-5—**Dynamic Psychotherapy Program.** University of Colorado Health Sciences Center at Aspen. Mon-Fri. Contact: U of Colo.

August 7-12—**19th Annual Primary Musculoskeletal Care Program.** University of Colorado Health Sciences Center at Breckenridge. Sun-Fri. Contact: U of Colo.

August 11-14—**Multimodality Approaches to Limb Salvage for Extremity Sarcoma.** P/SL Swedish Healthcare System at Westin Resort, Vail. Thurs-Sun. Contact: P/SL CME Office, (800) 633-6824.

August 14-17—**Fourth National Kaiser Permanente Emergency Medicine Conference.** Colorado Medical Society and Colorado Permanente Medical Group at Beavercreek. Contact: KPEM 94, PO Box 7131, Corte Madera, CA 94976-7131. (415) 927-7450.

August 15-20—**Breast Imaging and Intervention Into the 21st Century.** Radiology Imaging Associates at Broadmoor Hotel, Colorado Springs. Sun-Fri. Contact: Ryals & Associates, (404) 641-9773.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

Every Friday (except 4th Friday of month)—**Various Topics in Contemporary Medicine (Midday CME Series).** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

May 5-7—**Idaho Academy of Family Physicians 46th Annual Meeting.** Coeur d'Alene Resort, Coeur d'Alene. Thurs-Sat. Contact: Irma Sparks, Executive Director, Idaho Academy of Family Physicians, 777 N Raymond, Ste 100, Boise 83704. (208) 323-1156.

July 28-30—**Idaho Medical Association—Annual Meeting.** Sun Valley. Wed-Fri. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 22-23—**James Wiggins, MD, Lectureship.** Albuquerque Convention Center. Contact: Mary R. Boning, Presbyterian Healthcare Services. (505) 841-1225.

May 6-7—**New Mexico Medical Society Annual Meeting.** The Marshall Building, Albuquerque. Fri-Sat. Contact: Elsa Hall, 7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237.

July 18-22—**Imaging 1994.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

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CONTINUING MEDICAL EDUCATION

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August 7-11—**Lovelace Santa Fe Neurology 1994.** Eldorado Hotel, Santa Fe. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925, (404) 641-9773.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131, (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

May 18-20—**Odgen Surgical-Medical Annual Meeting.** Ogden Park Hotel, Ogden. Wed-Fri. 21 hrs. Contact: KayLynne, (801) 625-3122.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501, (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770, (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003, (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101, (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105, (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143, (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321, (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409, (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651, (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113, (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120, (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102, (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102, (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102, (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270, (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132, (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148, (801) 582-1565.

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WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

April 22-23—**Surgical Update 1994.** Tacoma. Fri-Sat. Contact: PCMS CME.

April 25-26—**Children's Justice Conference.** Bellevue. Mon-Tues. Contact: Children's, (206) 526-2501.

April 29—**Nuts, Bolts, and Innovation in Gastrointestinal Disease II.** Tacoma. Fri. Contact: PCMS CME.

April 29-30—**Mental Health Update.** Seattle. Fri-Sat. Contact: U/W.

May 6-7—**Cardiology Update.** Seattle. Fri-Sat. Contact: U/W.

May 8-11—**Fifth Annual Congenital Heart Disease in the Adult.** Stevenson. Sun-Wed. Contact: American College of Cardiology, (800) 257-4739.

May 13-14—**WCAAP—Issues for Washington Children.** Seattle. Fri-Sat. Contact: Children's, (206) 526-2501.

May 20—**Clinical Guidelines.** Tacoma. Fri. Contact: PCMS CME.

May 20-21—**Orthopedic Pathology Review.** Seattle. Fri-Sat. Contact: Children's, (206) 526-2501.

June 5-8—**1994 Annual Meeting of the Society for Vascular Surgery and the North American Chapter, International Society for Cardiovascular Surgery.** Seattle. Sun-Wed. Contact: SVS/NA-ISCVS, (508) 526-8330.

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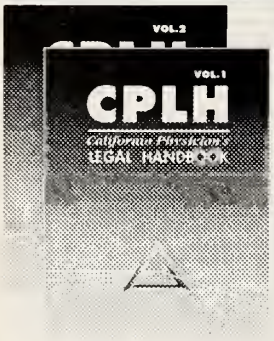

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Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below

Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli* and *Klebsiella* spp

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp and *Enterobacter* spp

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who received ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS).

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

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† Latest available annual data: January to December 1991

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

References: 1. Neu HC, Wilson APR, Grüneberg RN: Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5(2):67-93. **2.** Data on file, SmithKline Beecham Pharmaceuticals. **3.** Data from the Institutes for Microbiology Research, Franklin, Tenn. **4.** Neu HC: Contribution of beta-lactamases to bacterial resistance and mechanisms to inhibit beta-lactamases. *Am J Med* 1985;79(suppl 5B):2-12.

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Articles

Possible Interactions With Terfenadine or Astemizole

ANDREW D. ZECHNICH, MD; JERRIS R. HEDGES, MD; DIANE EISELT-PROTEAU, RPh; *and* DEAN HAXBY, PharmD, *Portland, Oregon*

Concurrent use of terfenadine or astemizole with erythromycin or ketoconazole can prolong the QT interval and produce potentially fatal ventricular arrhythmias. We examine the frequency and patterns of concurrent prescribing and suggest methods to reduce the incidence of serious drug interactions. By retrospectively reviewing Oregon Medicaid prescription claims data over 22 months, we determined the frequency of concurrent prescribing of terfenadine or astemizole with macrolide antibiotics or ketoconazole. From 1991 to 1992, terfenadine use increased by 29%, with a seasonal peak in June of each year. Terfenadine was one of the most prescribed medications from March through July 1992. During the 22 months reviewed, there were 122 episodes of concurrent use of terfenadine or astemizole with macrolide antibiotics or ketoconazole. Most of these episodes (94%) involved terfenadine. The frequency of concurrent use increased more than threefold from 1991 to 1992. Although patients received prescriptions from different physicians in 48% of these episodes, they used different pharmacies only 3% of the time. We demonstrate that terfenadine use is extensive and increasing, thus increasing the possibility of serious interactions, and many physicians may remain unaware of this potential. Effective prospective screening by pharmacists could dramatically reduce the incidence of concurrent prescribing. Physicians must be aware of the potential for these drug interactions, avoid prescribing these medications concurrently, and consider these interactions in the evaluation of syncope and cardiac arrhythmias.

(Zechnich AD, Hedges JR, Eiselt-Proteau D, Haxby D: Possible interactions with terfenadine or astemizole. West J Med 1994; 160:321-325)

Terfenadine (Seldane, Marion Merrell Dow) is a widely used nonsedating antihistamine approved for use in the United States in 1985 and taken by more than 100 million patients worldwide for symptoms of allergic rhinitis ("Dear Doctor Letter," Marion Merrell Dow Inc, August 6, 1990). Terfenadine was the tenth most prescribed medication in the United States in 1992.[1] Prolongation of the QT interval and serious ventricular arrhythmias (torsades de pointes) leading to syncope, cardiac arrest, or sudden death have increasingly been reported when terfenadine or astemizole (Hismanal, Janssen Pharmaceutica) is taken concomitantly with erythromycin or ketoconazole (Marion Merrell Dow Inc, oral communication, January 1993).[2,3] Case reports have detailed substantial interactions when terfenadine is used at recommended doses concomitantly with ketoconazole[2,3] or in patients with hepatic dysfunction[4] or acute or chronic overdose,[5-8] and recent clinical trials have confirmed the potential for prolonging the QT interval.[9] As of May 1992, about 80 serious cardiovascular events were reported to the manufacturer,[10] including cases of terfenadine overdoses and interactions with erythromycin, ketoconazole, and troleandomycin. The occurrence of notable interactions is probably underrecognized and underreported, however.

Similar adverse events have been reported with the use of astemizole, a similar nonsedating H_1-antagonist. Ventricular arrhythmias due to prolonging of the QT interval have been reported with astemizole use of 10 to 20 mg per day[11,12] and in patients with acute overdose,[13-16] and the manufacturer has made concurrent use with erythromycin, ketoconazole, or itraconazole a contraindication to astemizole therapy. Janssen notified prescribers of these adverse effects in July 1992 and announced the contraindications in a separate mailing in the fall of 1992 ("Dear Health Care Professional," Janssen Pharmaceutica, Oct 26, 1992).

Because of the serious nature of these interactions, considerable efforts have been made to inform health care

From the Departments of Emergency Medicine (Drs Zechnich and Hedges) and Family Medicine (Dr Haxby), Biomedical Information Communication Center (Dr Zechnich), Oregon Health Sciences University School of Medicine, Portland; the Drug Use Review of Oregon, Salem (Dr Zechnich, Ms Eiselt-Proteau, and Dr Haxby); and the Department of Pharmacy Practice, Oregon State University, Corvallis (Dr Haxby).

This investigation was supported in part by National Library of Medicine Informatics Training Grant 1T15LM07088.

Reprint requests to Andrew D. Zechnich, MD, Dept of Emergency Medicine, Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, UHN-52, Portland, OR 97201-3098.

ABBREVIATIONS USED IN TEXT

FDA = Food and Drug Administration
OMAP = Office of Medical Assistance Programs

professionals, but there is still concern that many providers remain unaware of the potential for serious sequelae. In 1990, Marion Merrell Dow Inc, issued a letter to 300,000 physicians and pharmacists reporting the possible consequences of interactions of terfenadine with ketoconazole or macrolide antibiotics ("Dear Doctor Letter," Marion Merrell Dow Inc, Aug 6, 1990). In addition to published case reports, these warnings were repeated in the *FDA Medical Bulletin* and *Drug Interactions Newsletter*.[17,18] Because it was apparent that concurrent prescribing of these medications continued (Marion Merrell Dow Inc, written communication, October 1992), the FDA issued a press statement on July 6, 1992, using national media coverage to announce the contraindication to concomitant use with erythromycin or ketoconazole. Since then, the FDA has reiterated the warnings in September 1992,[19] and the manufacturer has sent another 1.6 million letters to physicians and pharmacists in two separate mailings (Marion Merrell Dow Inc, oral communication, October 1992). The effectiveness of these measures has not been studied, and the magnitude of the problem of concurrent prescribing has not yet been reported.

The purpose of this investigation is to determine the incidence of concurrent prescribing of terfenadine or astemizole with macrolide antibiotics or ketoconazole and to examine possible methods to reduce the frequency of such interactions.

Methods

We retrospectively reviewed prescription claims under Oregon's Medicaid program between January 1991 and October 1992, which enabled us to ascertain the number of terfenadine and astemizole tablets prescribed and the number of episodes of concurrent use with contraindicated medications. To identify episodes of concurrent use, patients who received terfenadine or astemizole along with erythromycin, ketoconazole, or troleandomycin were selected by database query. The query analyzed prescription claims between January 1991 and mid-September 1992 and selected only patients who received both medications within 45 days of each other. For each of these patients, a profile was generated that included the date of dispensing, strength and quantity of tablets, prescriber, and dispensing pharmacy for all medications funded by Oregon Medicaid during the study period. One physician and two pharmacists reviewed these profiles independently to identify any concomitant use of these medications. An episode of concurrent use was defined as the prescription of a macrolide antibiotic (erythromycin or troleandomycin) or ketoconazole for a patient currently using terfenadine or astemizole, or vice versa. For the purposes of this investigation, any overlap of one or more days was considered important. The duration of therapy was calculated by the number of tablets prescribed, assuming the medication was prescribed at recommended doses. Although most episodes of concurrent use were independent pairs of prescriptions, any new prescription with the potential for interaction was regarded as a separate episode—that is, a patient receiving two erythromycin prescriptions during a single course of terfenadine was recorded as having two episodes of concurrent use. After the three reviewers reached consensus, data were transferred into a microcomputer database for analysis.

The Office of Medical Assistance Programs (OMAP) provides medical coverage for more than 220,000 Oregonians. Most of these patients—about 68%—are women.[20] A total of 10,000 to 12,000 health care professionals currently care for Medicaid patients, including 5,729 physicians (located both in and out of Oregon) and 1,349 dentists. Based on January 1992 data, there are 581 nonhospital pharmacies licensed by the Board of Pharmacy in Oregon. To receive reimbursement from OMAP for dispensed medications, pharmacists must submit a claim for each prescription dispensed under Medicaid funding. In 1991, approximately 2.5 million prescriptions were filled under this program in the state of Oregon. An information management company maintains the database of statewide prescription claims and responds to requests for information.

Results

Terfenadine and Astemizole Prescribing

Terfenadine was one of the top ten medications prescribed in our population during the months of March through July 1992, ranked by number of prescriptions per month categorized by the National Drug Code; in June 1992, it was the most prescribed medication by the National Drug Code. In our population, 542,563 terfenadine tablets (average, 45,214 tablets per month) were dispensed in 1991. The greatest usage was in June 1991 (61,147 tablets). In 1992, the number of terfenadine prescriptions increased: 593,863 tablets were dispensed between January and October (59,386 tablets per month). Figure 1 shows the seasonal increase in terfenadine use and the 29% overall increase from 1991 to 1992 (average monthly us-

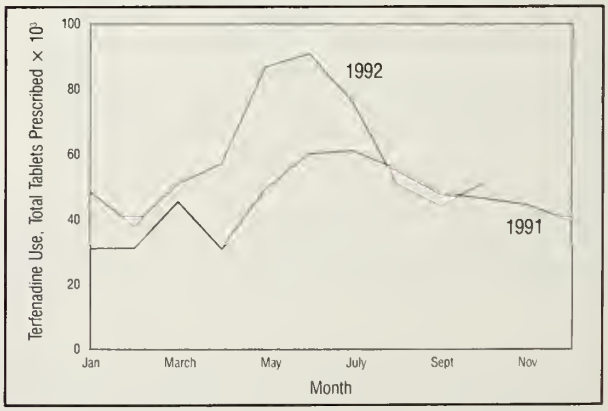

Figure 1.—The graph shows the number of tablets of terfenadine prescribed for patients covered by the Oregon Medicaid program between January 1991 and mid-September 1992.

age between January and October of each year). The most dramatic increases occurred in April and May, in which terfenadine use increased 85% and 77%, respectively, compared with the same months in 1991. Astemizole use demonstrated a similar seasonal pattern, with a total of 124,116 tablets prescribed between February and October 1992.

Concurrent Use

A review of prescription claims revealed 122 episodes of concurrent use of terfenadine or astemizole with a macrolide antibiotic or ketoconazole during the study period in Oregon's Medicaid population. Of these episodes, 115 involved terfenadine (94%) and 7 involved astemizole (6%). Of the 122 concurrent episodes, 29 occurred in 1991 and 93 occurred in 1992 (a 3.2-fold increase, Figure 2); 96 of 122 (79%) involved concomitant use with erythromycin, 13 (11%) with ketoconazole, and 13 (11%) involved troleandomycin. Although patients received prescriptions from two different physicians in 48% of these episodes, they used different pharmacies to fill the prescriptions only 3% of the time. In 29 (25%) of these episodes involving terfenadine, both prescriptions were dispensed on the same day. Of the 115 episodes, 22 involving terfenadine occurred after the FDA's media coverage of the contraindication on July 6, 1992. The mean number of days of overlap between concurrent prescriptions was 9.98 days. In four episodes (3%), the overlap was only one day. Concurrent use with metronidazole was incidentally noted in three of the study patients.

Prescribers

There were 69 different health care professionals who prescribed medications in these episodes of concurrent use, including 19 family practitioners, 12 internists, 6 general practitioners, 6 pediatricians, 5 internal medicine subspecialists, 4 dermatologists, 3 dentists, 3 allergists, 3 emergency physicians, 3 head and neck surgeons, 2 gynecologists, 1 general surgeon, 1 neurologist, and 1 whose specialty was unknown. Primary care physicians accounted for 59% of the prescribers involved in these episodes. No specific geographic pattern could be recognized. Distribution among rural and urban settings approximated the distribution of physicians in the state of Oregon.

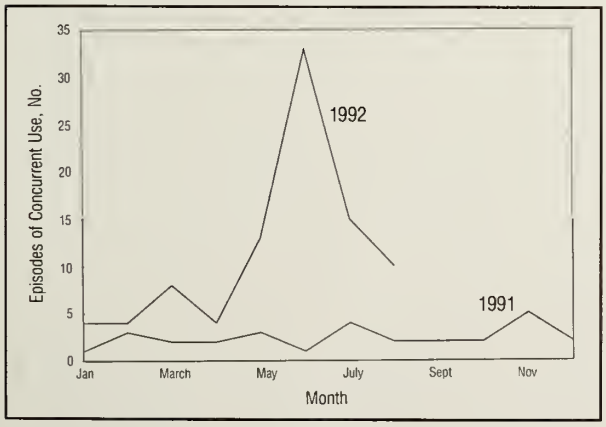

Figure 2.—The graph shows the number of episodes of concurrent use of terfenadine or astemizole with a macrolide antibiotic or ketoconazole in Oregon's Medicaid population from January 1991 through September 1992.

Pharmacies

In all, 38 different pharmacies dispensed medications involved in these episodes.

Patients

There were 40 different patients who received concurrent therapy. The average age of these patients was 40 years (range, 6 to 77), and 33 (82%) were women. The number of episodes of concurrent use per patient ranged from 1 to 24 (mean 3.0, mode 1, median 1). (The patient involved in 24 episodes was being treated long term with erythromycin by a dermatologist while receiving intermittent terfenadine therapy from two different otolaryngologists and a family practitioner.) The number of patients receiving concurrent prescriptions increased 4.75-fold from 1991 to 1992: 8 different patients in 1991 (average, 3.6 episodes per patient) and 38 different patients in 1992 (average, 2.4 episodes per patient). Many of these patients appeared to receive maintenance therapy with terfenadine as 20 of 40 patients received 200 or more tablets between January and September 1992, and 8 patients received 400 or more tablets (200 days of treatment) in this 273-day time period.

Discussion

This investigation found that terfenadine and astemizole use is widespread and increasing rapidly. Between March and July 1992, terfenadine ranked in the top ten medications prescribed in our population, as ranked by the National Drug Code; terfenadine prescription costs totaled $938,236 over the study period. Terfenadine use follows a seasonal pattern with heaviest use in May and June, and this seasonal variation was even more pronounced in 1992 (Figure 1). The number of terfenadine tablets dispensed per month increased 29% in 1992 compared with the same ten-month period of 1991, and the number of tablets dispensed in the month of May rose 77% over that of the previous year. This widespread use increases the number of patients at risk for possible interactions with other commonly prescribed medications such as erythromycin. Both terfenadine and astemizole are available without a prescription in Canada—although they are kept behind the counter and must be requested—and the FDA has considered over-the-counter availability in the United States.[21] Such action could dramatically increase the number of patients at risk.

The number of episodes of concurrent use of terfenadine with erythromycin or ketoconazole also increased markedly in 1992, as depicted in Figure 2. The number of episodes of concurrent use increased 3.2-fold from 1991 to 1992, and the number of patients involved in these episodes rose almost 5-fold, representing a pronounced increase in the number of patients at risk from these drug interactions. Because Oregon Medicaid covers about 9%

of the state's population, this study probably represents only a small fraction of patients receiving concurrent therapy in Oregon and a small proportion of those at risk nationwide.

Some physicians may remain unaware of the potential for interaction. In nearly half (52%) of the episodes of concurrent use, a single prescriber was responsible for both prescriptions. In 25% of the episodes, both medications were dispensed on the *same day*. Because this investigation examines prescription claims, the records reflect when a prescription is dispensed and not necessarily when a physician actually issued the prescription. In some of these episodes, the patient may have received a refill of a previously written prescription. A single primary provider should be aware of all medications currently taken by his or her patient, particularly when a new medication such as terfenadine or erythromycin is added.

How effective are "Dear Doctor" letters or national media coverage in informing physicians, changing their prescribing practices, and encouraging them to check their patients' medication profiles to prevent concurrent prescribing? Our investigation was not designed to measure whether physicians read the letters or incorporated the information into their practices, but our data suggest that informing physicians may have limited efficacy in preventing episodes of concurrent use. Despite considerable efforts to inform prescribers, concurrent use increased in Oregon. In 48% of these episodes, different physicians issued the medications. If a patient using terfenadine long term (as were many patients in our study) consulted a physician on an urgent, unscheduled basis, such as for bronchitis, that physician could issue erythromycin without having access to the patient's medical record. Even if an "informed" provider actively sought information about other medications, preventing concurrent use could rely on a patient's recollection of all of his or her current medications. Although educational efforts to alert physicians about possible interactions must be encouraged, the effectiveness of these efforts in preventing such interactions may be limited.

Recognizing pharmacists' responsibility to help prevent drug interactions, Congress included provisions in the Omnibus Budget Reconciliation Act of 1990 that require state Medicaid agencies to implement retrospective and prospective drug use review programs by January 1, 1993. These provisions specifically require that pharmacies screen at the point of sale for drug interactions, drug-disease contraindications, therapeutic duplication, incorrect dosage or duration of therapy, and drug-allergy interactions.[22] Most pharmacies use a computer system to monitor dispensing; as of mid-1991, 85.6% of 13,000 pharmacies responding to a survey indicated that they could screen electronically for drug interactions.[23] Few states have implemented a statewide system for such screening, however, and it remains uncertain how effectively possible interactions are detected by pharmacist review at the point of sale.

Our results strongly support an increased role for pharmacists in detecting possible drug interactions. Although patients received prescriptions from two different physicians in 48% of the concurrent use episodes, they used different pharmacies only 3% of the time. In other words, in 97% of these concurrent use episodes, the same pharmacy dispensed both medications involved in the possible interaction. As previously noted, both medications were dispensed on the same day in 25% of the episodes, presumably at the same time. Therefore, pharmacists have an excellent opportunity to reduce dramatically the potential for concurrent prescribing. Whereas most (85.6%) pharmacies report the capability to screen electronically for drug interactions,[23] our data suggest that some are not effectively detecting concurrent prescribing. With effective screening (prospective drug use review), as many as 97% of the episodes of concurrent use identified in this investigation might have been prevented.

Five patients were changed from terfenadine to astemizole just after the interactions with terfenadine received national media coverage. Although it has been less publicized, similar QT prolongation has been reported with astemizole use, and its manufacturer has also announced contraindications to concurrent use with macrolide antibiotics and ketoconazole.

The risk of adverse effects to a patient on concurrent therapy is difficult to estimate. Our investigation included four episodes in which the overlap in drug therapy was only one day, and the clinical importance of this degree of overlap remains unclear. In addition, there appears to be considerable interindividual variability in electrocardiographic changes with the accumulation of terfenadine.[9] Some prescribers may have elected to continue these medications in patients who had taken the combination previously without incident, although this practice should be discouraged. The lack of adverse effects from one episode of concurrent use does not guarantee safe concurrent therapy in the future. In any case, although the ultimate risk of adverse effects is difficult to quantitate in each episode of concurrent use, the frequency with which these medications were issued concomitantly remains disturbing.

Several weaknesses in this study should be acknowledged. First, our investigation measures only episodes of concurrent prescription and cannot assess the clinical consequences of these interactions. Second, by reviewing claims data, our investigation cannot determine how the medications were actually used by patients, but can only measure how they were dispensed. Some patients may have temporarily discontinued terfenadine use when issued a prescription for erythromycin, and others may have taken higher doses than recommended. Third, our study was not designed to estimate the effects of the most recent media coverage. Because the expected seasonal decline in antihistamine use occurred at the same time as the media release of the warnings, the incidence of concurrent prescribing in 1993 must be measured to estimate the relative effects of these two influences. Finally, complete data depend on the timely filing of claims by Oregon pharmacists, and the most recent data may be incomplete. Therefore, the incidence of concurrent prescribing in August and September 1992 is probably underestimated by our investigation.

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Articles

'Betelmania'
Betel Quid Chewing by Cambodian Women in the United States and Its Potential Health Effects

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Although an estimated 10% to 25% of the world's population chews betel quid, this practice is virtually unknown in the United States. Health care professionals coming into contact with immigrants and refugees from India, New Guinea, and Southeast Asia will increasingly notice this habit. Possible hazards associated with the chewing of the various ingredients of the quid include oral cancer and an addictive potential as strong as for cigarettes. We surveyed a group of Cambodian refugee women who are addicted to betel nut and its associated components. Participant-directed interviews uncovered some of the cultural meanings surrounding the ritual of preparing and using the betel quid and the role of culture in the beliefs and behaviors related to chemical addiction.

(Pickwell SM, Schimelpfening S, Palinkas LA: 'Betelmania'—Betel quid chewing by Cambodian women in the United States and its potential health effects. West J Med 1994; 160:326-330)

The areca nut, commonly known as betel nut, grows on an Areca palm tree (*Areca catechu*). Thought to have originated on the Malay Peninsula, it is the oldest known masticatory used by Asians.[1] Many older Cambodian refugee women in the United States chew betel nut quid, a combination of areca nut, betel leaf (from *Piper betle*), lime paste, and leaf tobacco. The women are easily identified because the quid causes the teeth to turn black-brown and stains the tongue and oral mucosa. The habit of betel quid chewing is not unique to Cambodian women, being common throughout Southeast Asia, India, and New Guinea. It is estimated that between 10% and 20% of the world's population chews betel.[1-3] Although the practice is uncommon in the United States, the prevalence of betel chewing has increased with recent waves of immigrants from Asia and Oceania and mystifies western health care professionals who know little of its use or associated health risks. We review and examine the current knowledge about the health risks associated with betel use, describe the beliefs and behaviors associated with betel use by ten Cambodian refugee women in San Diego, and offer an illustration of the conflicts that result when refugees and immigrants begin to acculturate.

Subjects and Methods

The Division of Family Medicine in the School of Medicine at the University of California, San Diego, supports a variety of cross-cultural clinical experiences for medical students. One of these experiences is with the Cambodian Home Health Care Project. Cambodian refugees receiving their health care in the Family Practice Clinics are referred to the project for follow-up examinations and health teaching, all of which are done in the home. Fourth-year medical students accompany the project director, a family nurse practitioner, and a Cambodian community aide on these visits. In the past 12 months, more than 150 home visits have been conducted in Cambodian households.

According to the 1990 census, there are approximately 4,185 Cambodians living in the city of San Diego. Although the prevalence of betel use in this population is unknown, a sample of 25 Cambodian residents 40 years and older participating in a health promotion class offered as part of the Cambodian Home Health Care Project revealed that all 12 of the 12 women but none of the 13 men attending the class chewed betel.

In February 1993, we interviewed the first ten Cambodian women encountered during home health visits to family members observed to be chewing betel. Nine of these women have chewed betel quid for many years. The women were between 40 and 81 years of age and had chewed betel for 29 to 77 years. Only one woman was a newcomer to the habit, having chewed for just three years. Characteristics of the women are summarized in Table 1.

A set of probe questions listed in Table 2 were developed for use in participant-directed interviews. The interviews were conducted on home visits by the family nurse practitioner coauthor of this article (S.M.P.) and another coauthor (S.S.) who is a female Cambodian translator, a licensed vocational nurse (LVN), and a trained commu-

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TABLE 1.—*Characteristics of 10 Cambodian Women in San Diego, California, Who Chew Betel Quid*

Subject	Age, yr	Age of First Use, yr	Belief in Heolth Risks	Report of Physiologic Effects	Believe Hord to Stop
1.....	40	11	Unsure	None	No
2.....	56	16	No	None	No
3.....	58	55	No	Yes	Yes
4.....	60	25	No	None	Yes
5.....	68	30	No	Yes	No
6.....	68	21	No	Yes	Yes
7.....	73	13	No	Yes	Yes
8.....	74	15	Yes	Yes	Yes
9.....	78	5	No	None	Yes
10	81	4	No	None	Yes

nity health worker. All questions in the interview format were translated by the LVN to the nurse practitioner, who then recorded the answers on paper. Additional questions asked by the nurse practitioner were translated into Cambodian by the LVN, who then translated the answers into English. The LVN reviewed all written responses to certify that they conformed with her understanding of the Cambodian answers to the questions asked. No men were interviewed because Cambodian men do not chew betel, preferring instead to smoke cigarettes.

Using a method described by Willms and colleagues, our analyses of the data collected during these interviews proceeded through three stages[4]: developing case studies; coding consensus, co-occurrence, and comparison; and abstracting cultural idioms. Particular attention was paid to the importance attached to each aspect of betel nut use by the respondents themselves. These data provided the basis for comparing the respondents' perspective with the perspective and preconceptions of the investigators. Caution should be exercised in evaluating these data because the sample was not selected at random and because the objective of the study was to identify content frames of investigation rather than to test specific hypotheses.

Results

The information obtained from these interviews is organized into categories similar to the questions listed in Table 2. These categories were reordered in the following manner to reflect the importance attached to each topic by the respondents themselves: the ritual of preparation, initiation, sex differences, physiologic effect, habit-forming potential, perceived health risks, cosmetic effect, and reaction of others.

Ritual of Preparation

In San Diego, Cambodian women, usually older than 50 years, chew betel quid composed of all four constituents: areca nut, betel leaf, red lime paste, and chopped tobacco leaf. Imported from Thailand and sold in cellophane bags, these ingredients are readily available in Asian markets. They are relatively inexpensive and do not appear to threaten the financial stability of the household.

The Cambodian word for the ritual of preparation and consumption of betel quid is *slamalou*, which means betel leaf. The ingredients for betel quid are stored in a hammered aluminum lazy Susan. The conveyance has several containers in which each component is stored separately. To assemble the quid, the lime paste is spread on the betel leaf, which in turn is wrapped around the areca nut slice. Tobacco may be wrapped as well, but is generally just placed between the gum and the cheek on the opposite side of the mouth from the quid. The quid and the tobacco are chewed for long periods of time, with much associated spitting. One of the women was edentulous and generally just gummed the hard nut; she sometimes pulverized it with a hammer after it was wrapped to enjoy the full flavor. Spittoons are fashioned from large cans lined with plastic bags. When the plastic bag is full, it is discarded and replaced by a new one. The house of the chewer has a characteristic odor easily identified as betel quid.

All but one of the women used the traditional components of sliced areca nut, whole betel leaf, red lime paste, and shredded tobacco (*Nicotiana tabacum*) to prepare the quid. We have also observed women extracting preassembled quid from their pockets to use when away from home. In this case they may not simultaneously use tobacco. Rather, they enfold the nut in the lime-spread leaf and wrap the preparation with a rubber band until they are ready to chew. Sometimes the leaf and the lime paste are placed in the mouth first, followed by one or more slices of nut, and then a pinch of tobacco.

The women were not self-conscious about the preparation and use of quid. When they were ready to prepare a quid, or spit out the juice, they did so regardless of visitors, meals, or conversation.

Initiation

A clear socialization process is apparent in the decision to start chewing betel. Although women who perceived themselves to be "addicted" to the mixture chew betel when they are alone, the habit arises from camaraderie with other women. Three women who started chewing in childhood (ages 4, 5, and 11 years) had the primary responsibility in their extended families of preparing the quid for their grandmothers. They became

TABLE 2.—*Interview Questions Asked of Cambodian Women About Betel Quid Chewing*

At what age did you start chewing betel nut and what influenced your decision to start?
Do you consider the practice in any way harmful to your health?
How do you feel when you chew betel?
Can you describe the procedure you follow when preparing the quid?
Are you bothered by the effect betel has on the appearance of your teeth?
How do you think others react to your habit of chewing betel?
If someone wanted to stop chewing betel, would it be hard to stop? Have you ever tried to stop?
Do you know any Cambodian men who chew betel? Why do you think this is a woman's habit?

curious, the materials for the quid were available, and they observed how much their mothers and grandmothers enjoyed this ritual. They said, however, that use was minimal during their youth, and as with the rest of the women, regular use did not begin until the late teens or twenties. The major contributing factor for the regular use of betel is childbirth. Young women at this time fully enter the social world of mature adulthood, as defined by motherhood. The women described their suddenly new relationship with their own mothers and grandmothers, as well as with neighbors of all ages and contemporaries who were also mothers. Only one woman started to chew in her later years. This 58-year-old said that only three years previously, her neighbor influenced her to join in preparing and enjoying a quid.

Sex Differences

The women considered smoking cigarettes to be a male prerogative and chewing betel to be a female habit. They saw this as sex-specific, and only two could recall seeing or hearing of men chewing. One said her grandfather was known to chew on occasion, and another said she thought men living in the Cambodian countryside sometimes chewed to be sociable, but she was somewhat hazy about this memory. One woman told us that smoking was "not normal" for women, but chewing "is normal." All appreciated the sociability of the ritual and the emotional connection it fosters with other women. Nine had learned the ritual of quid production from their mothers and grandmothers and one from her friend.

Physiologic Effects

Eliciting information about the physical effects of chewing experienced by the women was difficult. When asked this question, they each denied any effects. Further discussion indicated that our first inquiry was not well understood. Only a 74-year-old woman who had been chewing since age 15 admitted to the stimulating effect noted in physiologic studies. Two women mentioned the "sour taste" of the quid, but another noted that for her it had a bitter taste. The 81-year-old woman answered our question somewhat defiantly by saying "so good—yum, yum, yum." Three women made a connection between chewing after meals and the better digestion of food. One woman with exceedingly decayed teeth and swollen gums felt that chewing had an anesthetizing effect on her painful gums. All of the women had poor teeth, but Cambodian immigrants as a whole suffer substantial tooth decay and gum disease, so this cannot be blamed on the betel quid.

Apart from the constant chewing and spitting, betel nut use does not appear to produce any noticeable changes in behavior. Cambodians who do not chew betel quid see nothing unusual about the behavior of their betel-chewing relatives, friends, and neighbors.

Habit-forming Potential

Only the 58-year-old woman who had been chewing for just three years felt she did not have a dependence on betel quid. She could go several days at a time without betel. Although she occasionally chewed betel when alone, chewing seemed to be a social practice for her and generally confined to friendship. Everyone else admitted that the practice was highly addictive, and none of them showed any inclination to quit. They all thought that trying to quit would be difficult. Two of the women joked that they "would rather give up rice" than betel. One 68-year-old woman said she was so dependent that she chewed all day and frequently got up at night to prepare and chew a quid. The only time she had abstained in the 42 years since she acquired the habit was during an eight-day hospital stay. Although the hospital might have objected to the practice, she was entirely too ill to consider it (not unlike smokers when they are too ill to smoke). A 74-year-old woman who had been chewing since she was 15 years old said that the worst thing about being admitted to a hospital is the restriction on chewing. This woman was in ill health and was frequently admitted to a hospital for kidney disease and uncontrolled diabetes mellitus.

Betel chewing appears to be the only habit of these women. None of the Cambodian women seen through the Cambodian Home Health Care Project have reported or been observed using alcohol, opiates, or other drugs.

Perceived Health Risk

None of the women thought that chewing betel was a health risk, although most acknowledged that smoking tobacco causes lung cancer. They did not see an association between tobacco that is chewed and tobacco that is smoked. One woman related that whole tobacco leaf is safe but that shredded tobacco commercially rolled is unhealthful because it is not fresh. She also said that "back home in Cambodia," people grow all the ingredients for the quid in their own yards. Another woman who had recently returned from Thailand mentioned that she had brought fresh products back to California with her and found them far superior to the grocery store product. No one knew women who had oral lesions or sores on their lips, and they were unaware that in some parts of the world oral cancer is attributed to the areca nut and its associated components. The 40-year-old woman said she began having heart palpitations and subsequently decreased her betel use, but she did not blame betel for the rapid heart beat. Another mentioned that she never swallowed the juice produced by chewing the quid and carefully rinsed her mouth after chewing; she seemed to perceive this as a preventive health measure. She was the only one who said that she did not swallow—everyone else both swallowed and spit. All of the women were examined for oral lesions, and none were found.

Cosmetic Effect

All of the women with teeth had badly stained teeth. None of them perceived this as a problem to either their appearance or their dental enamel. Three thought that chewing the quid actually strengthened their teeth. None of the women we interviewed had good teeth. One woman told us that she thought the tobacco actually cleaned teeth and that she was in the habit of rubbing a

pinch of tobacco against her teeth while preparing the quid to protect her teeth against discoloration. She did not explain why her teeth were so badly stained despite this practice. A second woman described the effects of the tobacco component to be "like a toothbrush." Another seemed to think that good dental hygiene (scrupulous brushing) could keep the teeth from discoloring, but she was not concerned enough to do this.

Reactions of Others

All the women were aware that Americans disapprove of the habit, but it did not concern them. Two of the women were a little belligerent when expressing their unconcern with outsiders' disapprobation. Even the disapproval of health care professionals was dismissed. Through the years only once did one of us know a woman who went to a dentist for cleaning to rid herself of the stain. Whether or not she abstained from chewing in the future is unknown. The only time the women seemed slightly embarrassed about chewing was when we examined their mouths, throats, and teeth during home visits. They were concerned then only if they had a huge wad of partially chewed quid in their mouths. Otherwise the appearance of their teeth and gums caused them no embarrassment. One suggested that although Americans may be offended, Cambodians expect and accept the habit. For several women, stained teeth were a sign of maturity and of aging, a process that is much less threatening to Cambodians than to Americans. The woman who brought fresh quid components back from Thailand told us that she carried a small can aboard the airplane home, thoroughly enjoyed preparing and chewing the quid, and spit into the can in such an unobtrusive manner that no one around her was offended.

Discussion

Health Effects

Arecoline, a cholinomimetic alkaloid, is a major constituent of the betel nut. It is a potent diaphoretic; it stimulates the salivary, lacrimal, gastric, pancreatic, and intestinal glands and the mucosal cells of the respiratory tract; increases muscle tonus and plain muscle movement throughout the body; slows the heart rate; constricts the pupils of the eyes; and mimics the action of acetylcholine in the body.[3,5] The lime that is part of the betel quid hydrolizes the arecoline into arecaidine, a central nervous system stimulant that, in combination with the essential oil of the betel pepper (a mixture of phenols and terpene-like constituents), accounts for the euphoric properties of the betel quid when absorbed from the buccal mucosa.[6] The behavioral effects of the betel quid have also been attributed to arecoline as an inhibitor of the uptake of the neurotransmitter γ-aminobutyric acid.[7] Arecoline has been found to act as a bronchoconstrictor and has been implicated in high rates of hospital admissions of Asian immigrants for acute asthma.[8]

Areca nut extract has been found to be both cytotoxic and genotoxic and is widely implicated in the development of oral cancers.[9-12] The saliva of betel nut chewers has been documented to contain nitrosamines derived from areca nut alkaloids.[11-16] Oral squamous cell cancer is the most common malignant tumor in Papua New Guinea, a place where the practice of betel chewing is extensive.[8] It is also common in other parts of South and Southeast Asia where betel chewing is practiced.[9] The long-term health effects of continuous betel chewing remain controversial, however. The extrapolation of carcinogenesis data generated from in vitro laboratory experiments on animals to the human population often is complicated by altered pharmacokinetics and metabolic conversions and the presence of numerous confounders in humans.[12] Some studies have concluded that chewing betel without tobacco does not carry any significant risk for oral cancer.[2,17]

The betel vine leaf contains eugonal, an aromatic unsaturated volatile substance that is a central nervous system stimulant, and small traces of an alkaloid reputed to have cocaine-like properties.[8] Even without the addition of tobacco, the quid is thought to have possible mutagenic and carcinogenic properties[18] and was found to increase the normal intraoral pH of 6 to 7 to a pH of 9 to 12 within a minute after the chewing action commenced.[8]

Lime paste causes accelerated cell turnover by rapidly killing the cells with which it comes into direct contact. This continual turnover increases the likelihood of cell mutations. In areas of the world where the lime is added directly to the nut, instead of wrapped inside the betel leaf, and is then held directly against a specific site in the mouth (usually the right or left cheek), areas of malignant ulceration tend to form.[8]

When used as an ingredient of the betel quid, tobacco leaf carries the same risk for oral cancer as found in populations that chew tobacco alone. Smokeless tobacco use, as it is called in this country, is associated with an increased risk of oral cancer, periodontal disease, and cardiovascular disease.[19-22]

The addictive properties of the betel quid are reflected in withdrawal symptoms even among mildly habituated users.[23] In rare instances, heavy use of betel nut has resulted in an acute reversible toxic psychosis characterized by hallucinations and delusions.[24]

Betel Chewing Beliefs and Behavior

Asians and Pacific Islanders chew betel to enhance social interaction, suppress boredom, relieve tiredness, and increase work productivity.[3,25-27] In most Asian and Pacific Islander societies, betel chewing is practiced with little or no formal ritual in both public and private settings by men and women of all ages. It is frequently compared with cigarette smoking,[3] coffee or tea drinking,[25] or alcohol use[27] in the United States.

Our observations over many years of community work with Cambodian refugees indicate that the practice of betel quid chewing is widespread among women older than 50 and not unusual among women as young as 40. The prevalence of chewing is limited to women and is part of a socialization process learned at a young age. The symbolism extends beyond the obvious ritual of betel

quid preparation and includes female bonding, especially as it relates to motherhood. Chewing betel is understood to be a rite of passage from girlhood to womanhood. Even those women who experimented with the quid while very young (ages 4, 5, and 11) did not habituate until their late teens or twenties. The defining landmark for them was the birth of their first child. Whatever psychological dependence these women may have on betel quid cannot be attributed to the trauma experienced before or during their migration from Cambodia because for most of these women initiation occurred before these events.

Betel Chewing and Acculturation

Betel nut use reveals a number of aspects of the role of culture in the beliefs and behavior related to chemical addiction (alcohol, tobacco, and drugs).[28-31] The awareness of cultural meanings may cast new insight into clinical problems associated with addictions. This study also offers an illustration of the conflicts that result when refugees and other immigrants begin to acculturate and their traditional beliefs and behaviors are challenged by new beliefs and practices. None of the women in this study indicated any desire to cease the betel quid habit, and there is no widespread concern about the ill health effects of chewing the quid. Apparently oral cancer was not prevalent in Cambodia, and no adverse association has been made with any of the quid's ingredients. Nevertheless, we have been approached by three older Cambodian women who inquired about help to quit. These women were probably influenced by our concern about tobacco and smoking, expressed in our home visits and health promotion classes.

Although a habit like this is the norm in Cambodian society when women reach a certain age, it is not universally admired here in the United States. Young Cambodians consider it distasteful, and young women are not adopting the practice because they are taking on the norms of North American society and of their North American peers. During one of our interviews, a teenager and her boyfriend stopped to listen to our conversation. The young woman told us by word and by facial expressions that she was disgusted by the habit. She knew of no contemporaries who chew betel.

Although this is a habit confined to older women and is not apparently becoming a practice among young Cambodians in this country, the situation could conceivably change as teens enter their childbearing years. Regardless of its prevalence, health care professionals will for years to come see patients addicted to betel. As Cambodian women age, many more will come into contact with the health care system. Physicians will need information about the risk for oral cancers that long-term use can potentiate and should make a special effort to screen for oral lesions.

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Articles

Health Care in Armenia Today

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Although one of the smallest of the new independent states of the former Soviet Union, the Republic of Armenia has an ancient tradition and a strong ethnic identification, greatly enhanced by the diaspora. In addition to the problems following the dissolution of the Soviet Union, Armenia has had to contend with a draining war in Nagorno-Karabakh and the after-effects of a devastating earthquake in 1988. Humanitarian efforts have ranged from emergency supply deliveries to longer-term sustainable health care partnerships. The United States government, through the Agency for International Development, has organized such partnerships, partially as a result of a multinational mission in 1992 and a subsequent hospital-to-hospital program developed by the American International Health Alliance. We describe the current state of health care in Armenia and some of the problems that need to be addressed to improve health care services to its citizens.

(Farmer RG, Chobanian AV: Health care in Armenia today. West J Med 1994; 160:331-334)

The dramatic events following the dissolution of the Soviet Union affected the health care system of its 15 republics as it did all aspects of the society. In December 1991, US Secretary of State James Baker requested that humanitarian and other forms of aid to the new independent states of the former Soviet Union be organized and coordinated. As a result, a coordinating conference was held in Washington in January 1992 and attended by representatives of more than 50 countries. Five working groups were established for food, shelter, energy, medicine, and technical assistance. A delegation was formed that consisted of some 30 health care professionals representing 14 countries and international organizations. Ten republics were visited during the period of February 27 to March 31, 1992, to survey firsthand the medical and other health care needs of the new republics and to formulate recommendations based on the following four points of the action plan determined at the January 1992 conference:

- Emergency medical needs;
- Developing international health care partnerships;
- Assessing pharmaceutical manufacture, vaccines, and medical supplies, and the possibility of private and joint ventures in the health care support area; and
- Technical assistance needs including help with management and financial planning.

Health Care in the Former Soviet Union

The republics of the former Soviet Union have a highly centralized and well-organized health care system with a large number of health care professionals. Accessibility to health care services for the entire population, free of charge, is theoretically possible. The medical community has been isolated, however, and a rigid hierarchy has developed in the system over the years. Despite the breakup of the Soviet Union politically, this system remains largely intact because virtually all health care workers have known no other. Almost all have trained in their local region, and ethnic Russians are often in positions of authority, particularly in Central Asia. The "system" begins centrally, at the Ministry of Health or the city, at the state or oblast, or at the district or *rayon*, from whence the budget issues, and spreads peripherally.

One of the great shocks to the management of the system has been its separation from Moscow, as well as, of course, the disruption of the system that has been providing equipment, supplies, and especially drugs. Until 1991, budgets were centrally determined and health care facilities were given a fixed amount of money based on the number of beds in hospitals and number of visits in polyclinics. This formula sometimes varied for special circumstances such as "institutes" created in one or more fields, such as cardiology. The per capita population allocation has changed rapidly, and more leeway has been given to the managers, most of whom are physicians without any management training. Increased freedom in management has been offset by the loss of central funding from Moscow.

Long-term centralization has resulted in gigantic hospitals, with 1,000 to 2,000 beds being common, and polyclinics that see more than 1,000 patients a day, six days per week, in two 6-hour shifts. At the periphery of the system are smaller hospitals and polyclinics, down to

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feldsher (first-aid) stations, with thousands of nonphysician workers. It is here that primary care, including preventive care, immunizations, and maternal and child care, takes place. Patients are then transferred "up the line" as needed. Extensive ambulance systems that provide care on site are also common. There is no patient choice, little quality control, not much continuing education, and little of the medical educational structure familiar in many other countries. A small but growing private health care sector coexists with this hospital-clinic system. In many of the newly independent states, private practice is allowed, but often only in specialties not requiring hospital privileges.

Health Care in the Republic of Armenia

Nowhere have the adverse effects of the breakup of the Soviet Union been felt more severely than in the newly independent Republic of Armenia, which has also had to cope with the devastating earthquake of 1988 and the war between Nagorno-Karabakh and Azerbaijan. Our brief summary of the current health care system in Armenia is based on visits as part of the previously mentioned Medical Working Group Experts delegation to the new states (R.G.F.) and as a member of a team of experts sponsored by the American International Health Alliance that traveled to Armenia in September 1992 with the intention of developing hospital-to-hospital medical partnerships (A.V.C.).

The Republic of Armenia has a population of about 3.4 million, with about two thirds living in an urban setting. Life expectancy at birth in 1989 was 69 years for men and 74.7 years for women.[1] About 30% of the population is younger than 14 years.[1]

Cardiovascular disease ranks as the major cause of death, followed by cancers and pulmonary diseases.[2] Accidents represented one of the major causes of death in 1989,[1] and their number remains relatively high, in part because of the ongoing war. Infant mortality has been in the range of 20 to 25 deaths per 1,000 live births,[3] lower than the rates in many of the new independent states other than Russia, but higher than the values reported for developed countries. For instance, infant mortality in the United States is 9.8 per 1,000 live births (World Health Organization data, February 1994). Maternal mortality in Russia is also high, probably reflecting the use of abortion as the most common method of family planning—an average of five abortions per woman. Contraceptives are only infrequently used in Armenia.

Until recently, immunization practices in Armenia were broadly similar to those in the United States, with almost all children immunized against poliomyelitis, measles, diphtheria, pertussis, and tetanus. Because of the war and resultant blockade, however, vaccines are in short supply and immunization programs have broken down. Essentially no vaccines are currently being produced in Armenia.

Armenia has a large number of hospitals throughout the country, with an abundance of hospital beds for the population served. Some of the hospitals are tied to a state system and funded by the federal government, and others are municipal hospitals that are supported by cities. Under the Soviet system, some of the most advanced institutions were linked to Moscow and received their support from Moscow. Their funding was recently taken up by the federal government, and they are being added to the federal system. Many of the hospitals, particularly those in the major cities, deal primarily with specific specialties—pediatrics, obstetrics, infectious diseases, otolaryngology, cancer, rehabilitation, and specialized surgery, for example. As in the other newly independent countries, Armenia has a large number of polyclinics and other outpatient facilities, but these generally are not well integrated into the hospital systems. Networking between medical institutions continues to be poor, and links between the medical school and teaching hospitals are not well developed.

The medical facilities typically are more than 20 years old and in fair or poor repair. Some new hospitals and clinics have been built since the earthquake as a result of contributions from foreign countries and charitable organizations. Modern equipment is often lacking in the hospitals. For example, as of 1993, only one computed tomographic scanner was present in all of Armenia. Since the earthquake and war, routine medical supplies such as sterile bandages, disposable needles, syringes, surgical gloves, intravenous solutions, and many medications are in short supply. There is also a serious need for such items as autoclaves, anesthesia equipment, and large generators of electrical power. The last have become particularly important because of the frequent disruption in electricity.

Armenia has many physicians and nurses. There is currently approximately 1 physician for every 250 inhabitants, a number that is greater than that in most western countries. Salaries for physicians are low, only slightly higher than that of average workers. The quality of physicians varies. Under the Soviet system, strict medical school admission policies were not practiced, and frequently more than 1,000 medical students were admitted per year to the Yerevan Medical Institute. Armenian medical leaders are well aware of the need for establishing admissions and accreditation policies and are in the process of developing these. They also have begun reducing medical school class sizes. Students usually are admitted to medical school out of high school, with an average of five years being spent before a medical degree is obtained. Basic science training in medical school appears adequate, although students receive little hands-on clinical experience while in medical school.

Some medical school graduates may elect to have two years of residency. Specialty training following residency is of varying length. Training is not standardized, and accreditation board examinations are nonexistent.

Improved primary care and public health services are needed. Not surprising, considering the dire economic conditions, immunization programs have suffered greatly, and other disease prevention programs are generally lacking. Cigarette smoking is prevalent despite a high incidence of cardiovascular and pulmonary diseases.

Health care is financed primarily through a public system. Previous estimates are that only 3% of the gross national product is spent on health care, although the current figure is uncertain. Hospital support from the government is small, but is the major revenue source. The total support in 1992 for each of two large hospitals in Yerevan appears to have been less than $500,000 (US). Funding of hospitals depends both on the number of beds occupied and the total number of personnel. Because of the lack of other employment opportunities, officials are reluctant to eliminate jobs from the hospitals or elsewhere within the health care system.

New initiatives are being developed to provide privately financed medical care to the public, although private practice represents a small segment of health care. The Diagnostica Corporation is a leader in this regard and is now offering health care insurance to private subscribers. It is contracting with certain hospitals for the care of their insured patients.

The war with Azerbaijan and the earthquake of 1988 have placed additional stress on the health care system in Armenia. The genesis of the war over the Armenian enclave of Nagorno-Karabakh dates back to the Stalin era. The area is geographically surrounded by Azerbaijan territory but contains a majority of Armenians. There were about 200,000 of each nationality living in the other republic, but since the war, most have returned to their native republics, thus increasing the burden of refugees. The territory had been assigned to Azerbaijan in 1923, and the current war was perhaps precipitated by a petition in February 1988 by the residents of Nagorno-Karabakh that it be made a part of Armenia.[4] Since then, there have been many skirmishes and full-fledged battles, with thousands of civilian and military casualties.

Added to the already existing burdens of geographic isolation and the war in Nagorno-Karabakh, the earthquake on December 7, 1988, with a Richter scale reading of more than 9—greater than the San Francisco earthquake of 1989—created chaos. At least 25,000 people died (official estimate provided by Minister of Health of the Republic of Armenia, Dr Ara Babloyan, oral communication, March 1992), with other estimates varying upward to more than 60,000.[5] The most pressing medical problems immediately resulting from the earthquake included the trauma caused by falling buildings and other objects, the problem of crush injuries that resulted in acute renal failure, and the need for medications. Richards and co-workers summarized the experiences of a nephrology team from Great Britain,[5] who dialyzed as many as 70 patients a day. Of 800 patients admitted to one hospital, 460 had the crush syndrome. Many patients were sent to Moscow for treatment, but most were treated locally.

The medication problem was more difficult to solve. The immense task of getting a large amount of supplies to a distant location in the Causasus Mountains created staggering logistic difficulties. An estimated 500 tons of drugs and consumable supplies were sent,[6] but only 30% were immediately usable, and 20% had to be destroyed because they were outdated or did not have understandable generic names. For example, there were antibiotics with 238 different names, written in 21 languages, and often unknown to the health care professionals on location. The availability of drugs remains a serious problem. In view of the marked inflation and the devaluation of the ruble, which by mid-1993 had fallen to a value of less than 0.001 of a US dollar (versus about $1.3US before the dissolution of the Soviet Republic), purchases of medications, equipment, and supplies with foreign currency are now difficult, if not impossible.

The war-induced blockade, which has prevented most truck and rail passage to and from Armenia, has further complicated the situation. The past two winters were ones of bitter hardships. The fuel supply was blocked much of the time. When the Medical Working Group Experts delegation visited in March 1992, there had been unusually cold weather with temperatures of −10°C (14°F) on almost a daily basis. The huge concrete buildings had a refrigerator effect, and all meetings were held with everyone wearing overcoats and scarves. Furthermore, electricity was cut off about half the time, and lights (and electric heaters) would go on and off sporadically. In this past winter, the situation was even worse, with electricity averaging no more than two hours daily. Food was scarce, and food prices continued to rise rapidly. As a result, malnutrition has become a serious problem, particularly in children, and will remain so unless the blockade is lifted. In the earthquake zone, most of the inhabitants continue to live in huts and other temporary shelters. Refugees from the Nagorno-Karabakh war zone add to the housing problems. Drinking water in many areas has deteriorated in quality, as have the proper handling and storage of foods. Severe infectious diseases of the gastrointestinal tract have increased greatly in frequency, and cases of previously rare conditions such as brucellosis and botulism are being seen in notable numbers. In addition, tuberculosis is now rampant throughout the country.

Despite these serious problems, however, there is some cause for optimism regarding the future of health care in Armenia. A talented pool of professional personnel already exists in the country, and many persons are available for further training. The Minister of Health, his associates, and most of the medical leadership in the country appear dedicated to improving the health care system and the quality of medical care in Armenia. The Armenian diaspora is assisting in these efforts by providing substantial expertise and material aid. In addition, the American University of Armenia, which has been established in Yerevan under the sponsorship of the University of California, San Francisco, will soon be providing graduate courses in public health and health care management. Programs such as hospital-to-hospital partnerships that involve both public and private funding and the traditional governmental aid programs such as those funded by the US Agency for International Development have been established.

Working with the Armenian diaspora has greatly enhanced humanitarian efforts and health services planning.

As a result, the degree of isolation being experienced in Armenia is much less than that occurring in many of the other newly independent states, particularly those in Central Asia. An example of the identification of the Armenian diaspora with the problems of the people in Armenia is described in the response of children and adolescents in California to the 1988 earthquake.[7] There was "strong identification" with the victims as well as anxiety, made much worse when a similar earthquake occurred in the San Francisco Bay area less than a year later (T. Jones, "Double Jeopardy: Armenian Children in Bay Area Relive Terror of Soviet Quake," *Los Angeles Times,* October 22, 1989, vol 108, p A-3).

A recent article compared this area to the "Wild West," with a real risk of "carving up" the health care system, often for profit.[8] The need for a coordinated approach to health care, recommended by the Washington conference in 1992, is obvious, and developing hospital-to-hospital partnerships, as advocated by the medical experts group, is a valuable effort. The blending of professional experience, technical expertise, direct aid, and medical education can be of great benefit, particularly in Armenia. Although the costs are substantial, they pale by comparison with defense costs that have characterized the post-World War II era.

The tradition of free and accessible health care at all levels, from the first-aid station to preventive services, local hospital care, and specialty medicine, is an important part of the social fabric of the republics of the former Soviet Union. This tradition is admirable and should be preserved. The importance of the health care system to the stability of the new republics cannot be overemphasized. This applies particularly to Armenia, which, if given peace and stability, has almost unlimited potential because of its rich culture and the work ethic of the people.

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Articles

Role Modeling in Medical Education

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Role models play an important part in determining how medical trainees mature professionally. Demonstrating clinical skills at the bedside is the most distinctive characteristic of an effective role model. We discuss how role modeling affects professional identity and career choice and offer several suggestions for improving medical education, including the need for leaders to change the educational climate and culture. If implemented, these changes would enhance our ability to provide medical students with positive role models.

(Reuler JB, Nardone DA: Role modeling in medical education. West J Med 1994; 160:335-337)

American medicine and medical education are increasingly criticized for failing to meet the primary health care needs of patients and society. One cause of this shortcoming may be a relative lack of positive faculty models for students and residents. Although recent literature supports the importance of role models in medical education,[1,2] many physicians who teach do not seem to know how to effectively carry out this facet of their responsibilities. We briefly describe role modeling and its place in academic medicine.

Defining Role Models

Distinction should be made between mentors and role models. Mentors are older persons in an organization who take younger colleagues under their wings and encourage and support their careers. The mentor and protégé relationship is more continuous and complex than that of a role model. Mentors serve as friends and career guides promoting research and other academic activities, as information sources about expectations and strategies for advancement, and as intellectual guides providing collaboration on projects.[3] A mentor is an important transition figure who helps advance a protégé's personal growth and professional development, providing vision while helping the protégé to develop his or her own vision.[4]

A role model teaches primarily by example and helps to shape professional identity and commitment through promoting observation and comparison. Unlike mentors, role models may have only brief contact with physicians in training and do not so much deliberately mold students as inspire by their own conduct. Professional achievement, personality, power, influence, lifestyle, and values may all determine the influence a teacher has on a student.

Studies of outstanding clinical teachers reveal that those who interact skillfully with patients, providing supervision and demonstrating expertise at the bedside were more likely to receive high ratings from medical students.[5] In a study of an inpatient medical service, students judged attending physicians more on their clinical abilities as generalists than as subspecialists.[6] Other positive factors include self-criticism, assuming responsibility, recognizing limitations, humility, respect, and sensitivity for patients and trainees, and a wholesome sense of humor.[7,8]

Role Models in Medicine

Why is it important to discuss role models in medicine? Beyond the practical need to meet the call for more primary care physicians lies the ethical question of whether the issue of medical student abuse ought to be formally addressed.[9] This increasingly recognized phenomenon often involves negative comments about a trainee's career choice and thus sows self-doubt and confusion among students who may wonder, in the face of their own mistreatment by instructors, whether humanitarian impulses have a place in medicine.

Role models also play a substantial part in determining how students handle the transition from college graduate to practicing physician; how, in other words, they become socialized into the world of medicine. Each year of medical training raises new challenges, beginning with the need to feel comfortable talking and listening to patients, progressing to touching them, and ultimately to accepting responsibility for life-and-death decisions. At a time when the scientific mission of academic medicine seems to outweigh its commitment to the needs of individual patients and society as a whole, physicians who teach have the potential to rectify this imbalance by setting an example for students.

Not everyone agrees on the influence of role models. People differ in the degree to which modeling guides their behavior, determined in part by characteristics of the models and attributes of the trainees.[10] As more women and older students enter medical school,[11] it is legitimate to ask if faculties as they exist now can understand the needs of medical students and residents. Studies suggest

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that women may attach more importance than men to an interested role model and that they respond more to teachers who integrate professional and personal responsibilities.[12] The influence a role model has depends not only on observation, but also on the degree of similarity perceived by the student, raising the issue of what effect the preponderance of men among faculty members has on women students.[13]

Questions exist about the effect role models have on developing values. One investigator found that technical skills and knowledge were emphasized much more than values and that students and faculty differed in their values and attitudes.[14] An Israeli study found that teachers exerted little influence on students' values, concluding that models may merely reinforce views held at the start of training.[15]

What role do models play in the choice of a career? In the 1988 Association of American Medical Colleges (AAMC) graduation questionnaire, students deciding on internal medicine were most attracted by the intellectual and diagnostic challenge it presented, whereas those entering other specialties cited patients, work hours, and role models as being more important.[16] Are students going into internal medicine disillusioned with the residents, faculty, and practicing physicians who served as role models for them? The 1990 AAMC survey highlighted this issue, stating that students stayed away from internal medicine mainly because of the types of patients—elderly, chronically ill, terminally ill, self-abusing—and the perception that medical residents and internists are dissatisfied.[17] A recent study at our medical school (Oregon Health Sciences University, Portland) found a moderate effect of role modeling on specialty choice.[18] Of students selecting internal medicine, 70% identified a faculty member who had a positive influence on their choice; of those entering pediatrics and family medicine, 12% named a member of the faculty and 56% a community physician. Of those deciding on emergency medicine or anesthesiology, however, 33% identified an internist with whom they had an interaction so negative they decided to avoid a career in internal medicine. Of these negative role models, 60% were residents and 40% were faculty members.

Future Directions

As we look to the future, how should we think about role modeling? First, as others have noted, medical education is no longer the major activity of American medical schools.[19] Despite findings in the General Professional Education of the Physician report that general education continues to decline,[1] most medical schools still have not taken steps to correct deficiencies. To address this problem, we must reframe institutional goals, making education of students once again the highest priority of medical schools. This will require changing the basic culture of academic medical centers and restructuring financial resources. Leaders of institutions must clearly articulate the rationale for such change.

Excellence in clinical care must assume a higher place in our values.Too often there is a small, seemingly random chance that a medical student will be assigned to an effective and positive role model. Senior faculty practitioners should be organized into cadres of role models and be given incentives to invest the time and effort needed to fulfill this part of their duties. We can recognize teaching excellence in clinical medicine as a valued academic function by restructuring promotion and tenure guidelines.[20] In some institutions, this may be best accomplished by developing a two-track system, one in which faculty members are financially supported and evaluated based on research productivity and grants and a second that rewards effective teaching, investment in clinical activities, and curriculum development.

Those in leadership positions must acknowledge that role models may be negative as well as positive. If faculty development and personal counseling do not alter the conduct of those perceived to be negative role models, then that privilege should be withdrawn, other duties assigned, and financial support reconfigured.

We need to rethink where and how clinical medicine is taught. Is a hospital affiliated with an academic medical center the most appropriate atmosphere in which to train physicians? Professional growth, particularly at the student level, should include exposure to a mix of patients and problems typical of a community, not of the narrow focus of faculty practicing in a tertiary medical center. Highlighting medicine as a social good and acting with this in mind may help provide students with a stronger and more relevant foundation for practice. We should also strive to create a less stressful environment for residents in an effort to encourage them to serve as positive role models.[21]

Medical schools must respond to the needs of an increasingly diverse group of trainees by appointing clinical teachers more representative of the student body.[22-24] They should be given leadership positions and assisted in obtaining academic promotions. It must be recognized that the predominance of white men on the faculty of many medical schools may contribute to the stress that many female or minority medical students and residents feel.

Teachers of medicine should reaffirm the enormous influence role models have on education.[1,25] Positive role models pass on perspectives that may have broad and long-term effects for both patients and physicians.[25] We must be constantly aware that our behavior and attitudes influence students at all levels and that only through concerted effort, demonstrated at the bedside,[26] can we change their behavior and attitudes.

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* * *

MY MOTHER READING, GOING BLIND

Leaning toward the light like a tree
my mother holds an armful of crows
that fly up from the page to perch
on her hands, rove across her
rounded shoulders. She doesn't wince
when a bulging shadow scratches
her neck or when the corn-thief
cries deep in her ear.
With a magnifying glass, she examines
claws and feathers and beaks,
lingering over them.
When she's done and closes the book,
removing the thick glasses
that hide her eyes, the birds
vanish in a stream of smoke.
Don't worry, I can almost hear her say,
I see what I want. She turns,
her gaze falling over stacks of letters
and dusty photographs, blurry piles
scattered at her feet.

FRANCINE STERLE©
Iron, Minnesota

Articles

Epidemiology of Disaster
The Donner Party (1846-1847)

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I examined the pattern of mortality in the Donner Party, a group of emigrants who became trapped with inadequate food stores in the winter snows of the Sierra Nevada mountains in 1846-1847. The party consisted of 90 persons; the median age was 19.5 years (range, 1 to 70), 55 (61%) were male, and 72 (80%) were traveling with family members. Of the 90 persons, 42 (47%) died. Multivariate regression analysis indicated that age was the most important mortality risk factor. The lowest mortality (10%) was seen in the 6- to 14-year age group, and the highest was for persons younger than 6 years (relative risk = 6.6; 95% confidence interval [CI], 2.3 to 9.6) and persons 35 years or older (relative risk = 8.4; 95% CI, 3.4 to 10.2). Persons traveling without other family members had a relative risk of 2.0 (95% CI, 1.0 to 2.5). Men and boys were also at increased risk (relative risk = 2.0; 95% CI, 1.0 to 2.9). These factors can identify persons at increased risk for mortality in nutritionally stressed populations, and efforts to maintain intact family structures may improve survival.

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"Well, Ma, if you never see me again, do the best you can."

8-Year-old Martha (Patty) Reed, taking leave of her mother and rescuers to return to the cabin at Donner Lake to care for her 3-year-old brother.

Starvation is an enduring aspect of the human condition and reduces the capacity to withstand environmental stresses, including cold.[1] In the history of the American West, the experience of the Donner Party, a group of emigrants who became trapped with inadequate food stores in the Sierra Nevada mountains in the winter of 1846-1847, has fascinated generations with its tales of privation, cannibalism, and heroism. Despite the high level of interest in the Donner Party, little attention has been paid to epidemiologic aspects of the disaster and how factors such as age, sex, and social support affected survival. Although these events occurred nearly a century and a half ago, they hold contemporary relevance as political and natural upheavals cause starvation and forced migration in present-day populations.[2,3]

I briefly review the historical events and the results of an epidemiologic analysis of the Donner Party mortality experience using data abstracted from accounts of the journey.[4-9]

Historical Background

In the United States of the mid-1840s, population growth and economic instability led many to conclude that their futures lay farther west, in Oregon and California. Contributing to this view was the philosophy of "manifest destiny" that held that the United States would ultimately encompass the rest of the North American continent west of the Mississippi River. California was of particular interest because of its fertile lands and the likelihood that it would soon pass from Mexican possession. Thousands began to pack up their belongings in prairie wagons and gather in Independence, Missouri, to embark on the Emigrant Road.

Travelers risking their lives and fortune to travel west had a relatively narrow window in which to make the journey. They would have to leave in the spring and traverse the Great Plains to cross the Rockies and the Sierra Nevada, a mountain range in eastern California, before the winter snows. They were encouraged in their journey by expansionist politicians, newspaper editors, and pamphleteers. One of these was Lansford W. Hastings, whose book, *The Emigrants' Guide to Oregon and California*, proved fatally influential for the Donner Party.

The usual route for California-bound emigrants entailed a northward journey into present-day Idaho before turning south and west to California (Figure 1). Hastings championed a new route—The Hastings Cutoff—that appeared to shave 350 to 400 miles from the journey. He proposed leaving the main Emigrant Road at Little Sandy Creek in present-day Wyoming, proceeding to Fort Bridger, traveling south of the Great Salt Lake and through the Salt Desert, and rejoining the main California Trail in Nevada.

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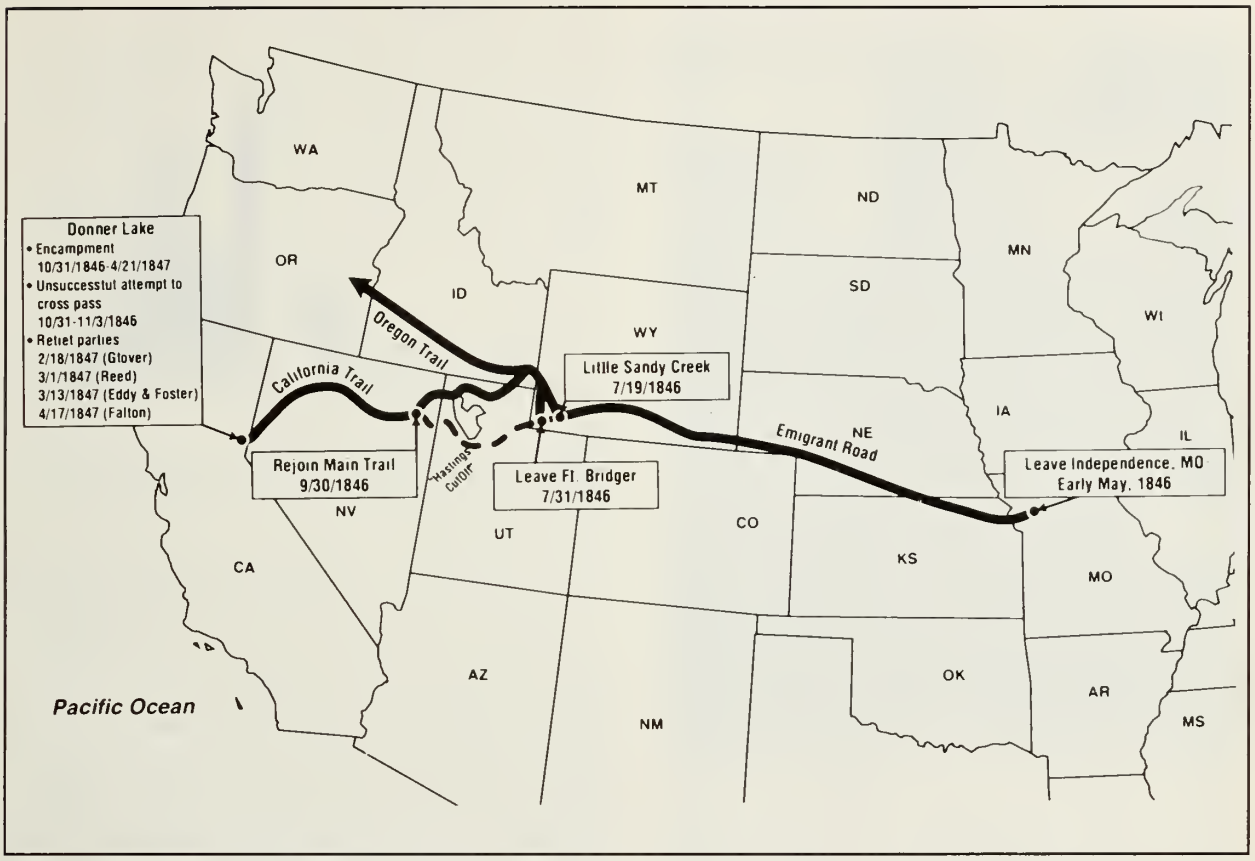

Figure 1.—The map shows the approximate route and dates of the Donner Party, 1846.

At Little Sandy Creek, a group of emigrants coalesced and made the decision to follow the Hastings Cutoff. Prominent among them was James Frazier Reed, a well-to-do businessman from Illinois. His mother-in-law, Sarah Keyes, had already become the first casualty of the group, having died of "consumption" (presumably tuberculosis) earlier on the journey. The company elected as their leader a prosperous farmer from Springfield, Illinois, Captain George Donner.

At Fort Bridger the emigrants stopped to rest in late July 1846. From there a connecting trail existed that represented their last chance to turn north and rejoin the main Emigrant Road. But many in the group had read Hastings's pamphlet describing the shortcut and, eager to push on, ignored warnings to rejoin the main trail. On July 31, 1846, the Donner Party headed west on the Hastings Cutoff.

Almost immediately, the group experienced unanticipated hardships. They had to hack a road through the Wasatch mountains, a task that took them about three weeks. Crossing the Great Salt Desert, which Hastings had described as a two-day journey of 40 miles, was in reality an 80-mile journey requiring five days. Finally they meandered through the Ruby Mountains of eastern Nevada before rejoining the California Trail. The "shortcut" took nearly two months of precious time and was actually 125 miles longer than the original Emigrant Road.

From the time the Donner Party chose the Hastings Cutoff, social cohesiveness unraveled as difficulties multiplied. One person was simply left behind to die when he became unable to walk and members were unwilling to carry him in a wagon. Arguments erupted. James Reed killed a man during an altercation. Initially threatened with hanging, he was banished from the party. He and a companion crossed the Sierra Nevada ahead of the company and before the winter snows. Ironically, his expulsion contributed to the party's salvation because he organized relief efforts that later brought in survivors.

Aware of their peril should they fail to cross the Sierra Nevada mountains before the winter snows, the remaining emigrants pushed on with increasing desperation. They had been weakened by the delay and had lost numerous oxen and wagons. Struggling through the early snows, the party reached the crest of the Sierras near Truckee Lake (now Donner Lake) on November 3, 1846. Exhausted from their ordeal and unable to go farther, they halted, intending to make the final crossing, now within sight, in the morning. These plans were soon dashed by a storm, as through the night of November 3 it snowed continuously. When the emigrants looked around them the following morning, they were surrounded by 3-m-high drifts of new snow. Defeated, they turned back to Donner Lake to establish camp.

The party now consisted of 81 persons huddled in makeshift shelters near the lake. Of the 88 persons who left Independence in the spring, 6 had died (3 of trauma,

2 of "consumption," and 1 abandoned in the wilderness), 3 had crossed the mountains in advance of the party, and the party had been joined by 2 Native American guides sent by Capt John Sutter.

As their situation grew increasingly desperate, a group of 15 members—10 men and 5 women—attempted to hike over the pass on snowshoes and on to Sutter's Fort in Sacramento, California. Calling themselves the "Forlorn Hope," the group left in mid-December, taking six days' rations. Beset by snowstorms and losing their way, they wandered for 33 days before coming to a small settlement. Eight of the men and none of the women perished. Those who lived survived only because they resorted to cannibalism and were able to kill game en route. In addition, they were helped by members of a Native American village. Ironically, the two Native American guides from Fort Sutter were consumed after probably being murdered by a member of the group.

With the arrival of this group of survivors, efforts for rescue attained new urgency. On February 18, 1847, the first relief party reached the lake. The rescuers surveyed a scene of misery and destruction. Corpses lay piled in the snow, and the survivors were gaunt skeletons, barely subsisting on boiled animal hides. Over the next two months, several relief parties journeyed to the camp. Because of the difficulty in reaching the lake, they were unable to bring in large stores of food and brought out only small groups of the strongest survivors. Paradoxically, the situation for those remaining grew more desperate, and the group resorted to cannibalism to survive. On April 21, Lewis Keseberg, the last remaining member of the party, left Donner Lake.

Materials and Methods

Accounts of the Donner Party experience were reviewed to determine sex, age, and whether or not traveling with other family members in the party.[4,6-9] Families traveling with married children and grandchildren were considered one family unit. The senior Donner brothers were each married with children and were considered separate family units. Data were entered into a VAX 3100 computer and analyzed using procedures available in the SAS software system.[10] Age was categorized as 5 years or younger, 6 to 14, 15 to 34, and 35 or older. Group comparisons for age were made using the Wilcoxon test; group comparisons for categorical variables were made using the χ^2 test.[11] Subsequent stratified analysis revealed no evidence of interactions, and logistic regression using a main effects model was employed to examine the association between mortality and possible risk factors.[11] Data were complete for all but two subjects for whom age was unavailable; these subjects were excluded from the final multivariate analysis. The adjusted odds ratio estimates were converted to adjusted relative risk for mortality (mortality ratio), using as reference the category with the lowest mortality rate for each variable.

TABLE 1.—*Demographic Characteristics and Mortality of Donner Party, 1846-1847*

Characteristic	Frequency, n (%)	Mortality Rate, n/N (%)	Adjusted Mortality Ratio* (95% Confidence Interval)
Number in party	90 (100)	42/90 (47)	--
Age, years			
Unknown	2 (2)	2/2 (100)	--
≤5	19 (21)	11/19 (58)	6.6 (2.3-9.6)
6-14	21 (23)	2/21 (10)	1.0†
15-34	34 (38)	16/34 (47)	3.3 (0.7-7.8)
≥35	14 (16)	11/14 (79)	8.4 (3.4-10.2)
Sex			
Male	55 (61)	32/55 (58)	2.0 (1.0-2.9)
Female	35 (39)	10/35 (29)	1.0†
Traveling with family members			
Yes	72 (80)	27/72 (38)	1.0†
No	18 (20)	15/18 (83)	2.0 (1.0-2.5)

*Computed as relative risk for mortality in reference to the category (†) with lowest mortality rate, adjusted for simultaneous effects of age category, sex, and whether or not traveling with other family members.
†Reference category.

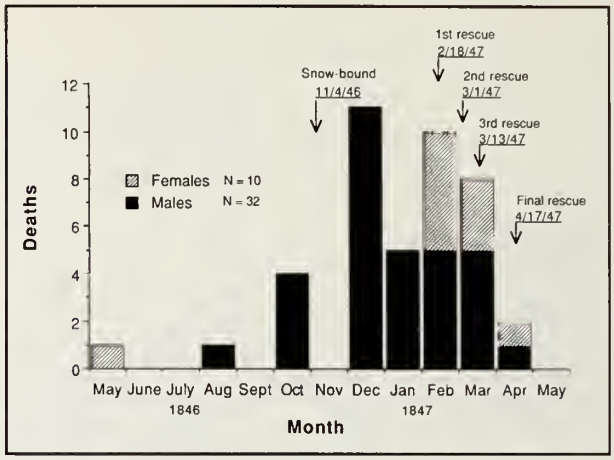

Figure 2.—The graph shows the mortality distribution, deaths by month and sex.

Results

There were 90 subjects (Table 1), including James Reed's mother-in-law, who died crossing the plains, and two Native American guides (Luís and Salvador) sent to the Donner camp by Capt John Sutter. There were 11 family groups ranging in size from 2 to 13 persons (median 7) and consisting of 72 persons. The other 18 persons (20%) traveled without family members; all were adult men. The median age was 19.5 years (range, 1 to 70). Survivors were younger than those who perished (16.4 years versus 26.0 years; $P < .05$), and persons traveling with family members were younger than those traveling alone (18.8 years versus 29.5 years, $P < .001$). Female members were younger than male members, but the difference was not significant (mean, 18.8 versus 22.0 years).

Of the entire party, 42 died (Figure 2). Survival rates were higher for women, the 6- to 14-year age group, and persons traveling with other family members. Among

subjects who died, female members survived longer than male members, and their deaths were more likely to occur in the latter half of the mortality distribution ($P < .01$). Multiple logistic regression analysis (Table 1) indicated that age exerted the strongest effect, with the highest mortality for those younger than 6 years and persons 35 years or older. Male sex was also independently associated with a twofold increased risk for mortality. The increased risk for men and boys persisted even after removing the group of men traveling without family members. Although persons traveling without other family members also showed a twofold increased risk for mortality, this reflects the experience of adult men because all women and children were traveling with a family member. In comparison with women in the two older age categories, men traveling without family members had a relative risk of 2.6 (95% confidence interval 1.7 to 2.8). Among those traveling with family, there were no significant differences in survival between the family groups, and family group size did not exert a clear effect.

Discussion

This report examines the mortality experience of a well-known historical disaster involving a group of 90 persons traveling to California in 1846. The most important risk factor from the multivariate analysis was age. Traveling without other family members and male sex were also important, and each carried a twofold increased risk. The analysis reflects the experience of the entire party, although not all members participated in the complete journey. Physical hardship and nutritional deficiency exerted a winnowing effect throughout the entire travail of nearly a year. A number escaped the most harrowing experiences at Donner Lake through early death or good fortune, whereas the two Native American guides joined the group late and perished in its fatal denouement. Because survival was affected by the exposures and tribulations associated with the journey, I have included all members in the analysis. Limiting analysis to the 81 members entrapped at the lake yielded substantively similar results.

The immediate cause of death cannot be ascertained for most of the subjects. Although several deaths were related to trauma, most were due to complications of starvation and hypothermia or other rigors associated with their ordeal. Starvation causes a reduction in the basal metabolic rate and a loss of body mass, reducing the ability to maintain body temperature in cold environments.[12] Starvation also increases susceptibility to infection,[1,2] and this was a known or likely factor in several deaths. A vitamin deficiency disorder, such as scurvy, may also have contributed, although I found no mention or suggestion of this in historical accounts.

The elevated death rates for persons at the extremes of the age distribution have been observed in other studies of nutritionally stressed populations.[1,2,13] Famine in cold climes occurred during World War II in several locations, including Leningrad and parts of Holland,[12,13] and younger and older age groups were disproportionately affected.

Figure 3.—A statue was erected to commemorate the Donner Party at Donner Lake. The pedestal shows the height of the snow (6.7 m, or 22 ft) in the winter of 1846-1847.

Recent experience in refugee camps in Somalia during an eight-month period of the 1992 famine documents a death rate of 74% for children 5 years and younger, a twofold to threefold increase over that of persons older than 5 years.[14] The increased risk for early childhood and older age groups is probably due to a reduced ability to provide for oneself and to adapt to nutritional, physical, and infectious stresses.

Improved survival was seen for persons traveling with family members, and the basis for this is unclear. It appeared that members of family groups formed strong support networks, saving food and other provisions for their members rather than sharing them with the group. Persons traveling alone did not have the benefit of these networks, and the cohesiveness and support provided by the Donner Party as a whole was weak. Selection bias may also have been present, in that persons traveling alone may have been less fit physically or psychologically than persons traveling with family members.

Men had an increased risk for mortality after adjusting for the effects of age and traveling with family members. The gender effect was most striking in the group attempting to snowshoe out in mid-December; all five women and only two of ten men survived. Survival advantage for starvation-affected women has been reported in other population groups[12] and in studies of animals.[15] The basis for this is unclear, but may relate to an increased loss of protein and lean body mass in nutritionally stressed men.[15] In addition, women have lower daily caloric needs and maintain a higher percentage of body

fat,[12] which may help them to survive in conditions of cold and starvation. Sex-related behavioral differences—that is, performance of high-risk or strenuous tasks—may also play a role.

Cannibalism is one of the best-known aspects of the disaster, but its effect on survival is difficult to ascertain based on these data. Because of the strong social stigma attached to it, information may not be reliable. In addition, the likelihood of engaging in cannibalism is related to the extremity of the situation. Persons dying early would not have had the same opportunity to engage in cannibalism because of the time needed to break down social taboos against it. Cannibalism clearly provided a source of nutrition, and it is obvious that the members of the "Forlorn Hope," who wandered for 33 days, having taken only 6 days' rations, would not have survived had they not consumed those who died. On the other hand, the two family groups with the highest survival rates (the Breens and the Reeds, all of whose snowbound members survived) are considered not to have engaged in cannibalism.

Although the Donner Party disaster occurred nearly 150 years ago, it retains contemporary relevance because the factors associated with increased mortality likely have a biologic basis or are due to enduring behavioral characteristics. Two risk factors for mortality observed in this study—age and male sex—cannot be altered or mitigated, but they may be used to identify high-risk groups in starvation-affected populations. The observation that family structure was an important independent determinant of mortality also suggests intervention strategies for similar disasters. Specifically, measures to keep family groups intact so they may draw on their internal support network may improve survival.

Epilogue

Nearly a century and a half have elapsed since the Donner Party disaster, yet the story possesses an enduring power and immediacy. The last members of the original party survived into the 1930s, well within the scope of living memory. These events have left many visible threads in the fabric of the West. Truckee Lake was renamed Donner Lake. A museum and memorial statue showing the depth of the snow (6.7 m) in that winter of 1846-1847 (Figure 3) have been established near the encampment. No winter of similar severity has occurred since.

Several members of the party went on to become prominent figures in California. Patrick Breen kept a diary that provides an invaluable firsthand account of the disaster; this document is kept at the Bancroft Library at the University of California, Berkeley. James Reed became a leading citizen in San Jose. His daughter, Martha (Patty), had weakened during an initial rescue attempt and had to return to Donner Lake, subsequently to be rescued by her father. Throughout her journey she carried a doll, which is now on display at Sutter's Fort in Sacramento.

An interesting historical footnote is that the last person to be rescued from the site, Lewis Keseberg, was vilified by a public deeply offended, in part, by his uninhibited and lurid descriptions of his cannibalism during the ordeal. He settled in Sacramento and opened a restaurant—an ironic career choice, considering the basis for his notoriety. He died in 1895, at the age of 81, at the Sacramento County Hospital, which later became the University of California, Davis, Medical Center.

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Conferences and Reviews

Melanoma Risk Factors and Atypical Moles

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Despite important advances in the treatment of melanoma, the prognosis for advanced disease remains discouraging. This fact, in combination with a worldwide epidemic of melanoma among persons of white skin type, has focused attention on identifying melanoma in its early, surgically curable stages. Attention has also been directed toward pinpointing which persons are at increased risk for melanoma to reduce risk where possible and to aid early diagnosis. Essentially all epidemiologic studies have identified an increased number of melanocytic nevi as an important risk factor in the development of melanoma, but controversy has arisen concerning the risk associated with certain types of nevi, particularly "dysplastic" nevi. We review melanoma risk factors and examine the relationship between melanocytic nevi and melanoma to clarify for primary care physicians what is "known" (noncontroversial) and what is "unknown" (controversial). We propose a working definition of an atypical mole phenotype and outline an approach to managing high-risk patients.

(Williams ML, Sagebiel RW: Melanoma risk factors and atypical moles. West J Med 1994; 160:343-350)

An increased incidence of malignant melanoma is easily documented from various areas of the world.[1-3] Melanoma has been of interest to epidemiologists, pathologists, and clinicians in this regard for many years. Incidence rates have doubled each decade for the past two decades.[2] The death rate has also increased, but at a much lower rate—about 5% per year.[2] A decade ago the most rapid increase in the incidence of melanoma occurred in the lower legs of women in the 40- to 60-year age groups. Currently the most rapid increase in incidence is occurring in older persons, primarily older men, in the head and neck regions.[4] The increased incidence of melanoma has been attributed in part to earlier diagnosis because the five-year survival of melanoma patients has dramatically improved. For example, in 1960 the five-year survival of patients with malignant melanoma was 40%; in 1990 it was 83%.[2] The increase in incidence and survival cannot be attributed to either a change in diagnostic criteria or to a change in disease definition[3]; it appears to be a real event.

Melanoma is also of interest because it begins on the surface of the skin, is commonly associated with melanocytic nevi (moles), and is usually pigmented. The observation of precursor and early lesions affords the opportunity to interrupt tumor progression at a curable stage of evolution. As many as 80% of patients with melanoma report a change in a preexisting mole.[5] Yet, considerable controversy has surrounded the frequency with which melanomas are histologically associated with melanocytic nevi.[5-7] Whereas in most studies only a third of melanomas arise contiguous with benign nevi, several factors may affect these estimates, including tumor thickness (larger tumors may obliterate the preexisting nevus) and whether the entire lesion is examined stepwise. A recent review of the University of California, San Francisco, Melanoma Clinic data base revealed that more than 50% of primary melanomas arose in histologic association with a precursor nevus.[8] Furthermore, when only thin tumors were analyzed—less than 1.5 mm in tumor thickness—where the likelihood of obliteration would be less, 64% of primary melanomas were associated with precursor nevi.

Risk Factors for Melanoma

Differentiating persons at increased risk for melanoma and identifying the factors that underlie that risk should both enhance the diagnosis of early melanoma through close surveillance of high-risk persons and point to opportunities for reducing risk. Several studies have identified melanoma risk factors by comparing melanoma patients with control groups, from which composite relative risk tables have been constructed (Table 1).[1,9-22] The relationship between acquired nevi, both common and "dysplastic" (atypical) types, and the development of malignant melanoma is the primary subject of this review. Appropriate management of at-risk patients, however, requires an overall assessment of their melanoma risk factors.

The predominance of lightly pigmented persons in the melanoma population, as determined by skin, eye, hair

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TABLE 1.—*Melanoma Risk Factors*†

Factor	*Estimated Relative Risk*
Changing pigmented lesion	Very high
Xeroderma pigmentosum	500
FAMM syndrome kindred	
Previous melanoma	500
Atypical nevi but no previous melanoma	150
Numerous common nevi	5-65
Atypical nevi	7-20
Giant congenital nevus	5-15
Previous melanoma	9
Lentigo maligna	5-10
Immunosuppression	4-7
Sun sensitivity	2-3
Excessive sun exposures	2-4
Melanoma in first-degree relative	2-12
Few or no common nevi	0.3
Hispanic or African-American persons	0.08-0.15
Age <15 years	0.01

FAMM = familial atypical mole or melanoma

*Average risk = 1.

†Estimates are derived from Koh[1] and Rhodes et al[9] and modified by data from Roush et al,[10] Evans et al,[11] Kraemer et al,[12] Greene et al,[13] Weinstock and Sober,[14] Greene et al,[15] Nordlund et al,[16] Halpern et al,[17] Garbe et al,[18] Rhodes et al,[19] Quaba and Wallace,[20] and Kaplan.[21]

color, or a history of sun sensitivity, is striking.[23,24] In contrast, persons of more darkly pigmented races have a low incidence of melanoma, and in them melanomas predominate on unusual sites, such as palms or soles and mucous membranes.[25] An association between melanoma and excessive exposure to sun or cutaneous signs of chronic actinic damage has been repeatedly noted.[11,26,27] The predominant sites of melanoma, however, are those exposed to intermittent, intense sunlight, such as the back (men) and legs (women), and not those receiving more constant exposure, such as the face and dorsal hands and forearms, that are favored by the epithelial malignant tumors, squamous and basal cell carcinomas.[26,28] Similarly, several epidemiologic studies have linked brief intense sun exposures, such as severe sunburns, especially during childhood or in relation to sun vacations, to increased melanoma risk.[27,29-32] Indeed, the increased incidence of melanoma associated with higher socioeconomic status or educational level[29,33,34] may derive in part from the penchant of the affluent for sun vacations.[11] Finally, patients with xeroderma pigmentosum, an autosomal recessive trait of impaired DNA repair to ultraviolet light injury, have a high risk of melanoma.[12]

Immunosuppression, including human immunodeficiency virus infection, has also been linked to an increased incidence of melanoma.[13,35] Moreover, melanomas may be more aggressive in these patients.[13]

The remainder of the known melanoma risk factors listed in Table 1 relate to melanocytic nevi. Large congenital melanocytic nevi—nevi greater than 9 cm in diameter—are uncommon, occurring in less than 1 in 20,000 births,[36] but carry a substantial lifetime risk for melanoma (relative risk, 5 to 15).[37-39] The management of these patients is complex due to the size and extent of their lesions and the propensity for melanoma to develop during childhood and at unusual sites, such as the central nervous system.[40,41] The melanoma risk associated with more common (occurring in about 1% of newborns), small congenital nevi is controversial,[37] due to the absence of reliable criteria to distinguish them from other nevi in adults.[42,43] At present it may be prudent to consider removing small congenital nevi if their clinical features are such that early detection of melanoma would be difficult—for example, very dark or variable color and topography or difficult-to-observe site—and if the patient has other melanoma risk factors.

Lentigo maligna macules carry a 5% to 10% risk for the development of an invasive melanoma.[14] They are recognized clinically as an expanding, irregularly pigmented macule in middle-aged and elderly adults with ongoing exposure to sun and histopathologically by the proliferation of atypical melanocytes within the basal epidermal layer.

Acquired Nevi and Melanoma Risk

A major risk factor for melanoma in virtually every study has been the presence of numerous acquired melanocytic nevi, although the magnitude of the estimated risk varies considerably between studies.[11]* In general, the higher the nevus counts, the higher the risk. Moreover, several studies noted increasing risk in relation to increments of nevus numbers (Table 2).[32,44-49] Taken together, these and other studies indicate that melanoma risk is roughly proportionate to the number of melanocytic nevi.

Thus, although it is well established that high mole counts characterize persons at increased risk for melanoma, the nature of the relationship is controversial. There is disagreement about the percentage of melanomas that appear to arise from preexisting nevi histopathologically, with estimates ranging from about 20% to as high as 64% for thin melanomas (discussed earlier). Because the age distribution of acquired nevi and melanoma differs—that is, nevus counts decline after age 50,[50,51] whereas the incidence of melanoma continues to rise with advancing age—this might further suggest that they are unlikely to be histogenetically related. The proliferation of melanocytes at the dermoepidermal junction (junctional activity) is more common in the moles of younger people, whereas moles in older people atrophy and ultimately disappear. On the other hand, older patients with melanoma have junctional proliferation associated with their melanomas, and the "activation" of nevi in the region of the primary melanoma has been noted.[52] Thus it is possible that patients in whom melanomas develop have abnormally persistent junctional activity in their moles. Junctional proliferation in clinically atypical (dysplastic) nevi is known to persist in later life.[52]

Body sites with higher mole counts are preferential sites for the development of melanoma.[46,53] Both melanomas and nevi of either the common or dysplastic types

*See also the editorial by R. L. Barnhill, MD, "Moles and Melanoma—New Method in the Madness," on pages 381-384 of this issue.

TABLE 2.—*Relative Risk of Melanoma in Relation to Number of Benign Nevi*

Study	Country	Nevus Definition	Nevus Counts	Relative Risk
Holly et al, 1987[44]	United States	≥2 mm, whole body "nondysplastic"	11-25	1.6
			26-50	4.4
			51-100	5.4
			>100	9.8
Weiss et al, 1991[45]	Germany	"Benign" nevi	10-50	4.3
			>50	14.9
Krüger et al, 1992[46]	Germany	≥2 mm, trunk (men)	5-10	2.9
			11-20	5.5
			>20	32.6
			>40	133.4
Swerdlow and Green, 1987[47]	Scotland	≥2 mm, whole body	10-24	4.4
			25-49	8.7
			≥50	63.8
Green et al, 1985[48]	Australia	≥2 mm, left arm	2-4	15.7
			5-10	14.9
			>10	20.1

predominate on sites receiving intermittent, rather than constant, sun exposure, with the lowest numbers occurring on sun-shielded areas.[26,28,46,53-56] These observations suggest that even if melanomas do not invariably arise from preexisting nevi, both may arise through common stimuli, the most likely source according to epidemiologic studies being sunlight exposure. The strongest evidence for a relationship between sun exposure and melanocytic nevi derives from studies correlating the number of nevi with age at the time of immigration to sunny climates; higher mole counts were associated with immigration during childhood.[57,58] Occasional anecdotal accounts of nevi occurring in sites of previous severe sunburn provide further support for such a relationship (R.W.S., unpublished observations, August 1993).

Most studies also note higher mole counts in light-skinned persons.[54,56,57,59-61] Whether this relationship derives solely from the increased sun sensitivity of light-skinned persons or points to other genetically determined factors is unclear. Twin studies have provided strong evidence for a genetic factor(s) in determining nevus number, by demonstrating that mole counts are similar in identical, but not in fraternal, twins.[62] An increased number of melanocytic nevi are also reported in the chromosomal disorders Turner syndrome (XO)[63] and ring chromosome 7 syndrome.[64] Finally, an increased number of nevi has been reported in children following renal transplantation[65] or chemotherapy for a malignant tumor,[66,67] suggesting that immune function is an additional determinant of nevus numbers.

In summary, it appears that environmental (sun exposures), physiologic (immune function), and genetic factors determine the number of melanocytic nevi that will develop in a person. In view of the strong association between nevus number and melanoma risk, reducing sun exposures during childhood would be expected to substantially reduce this risk. Furthermore, children at increased risk for numerous moles—fair-skinned children or those with a family history of either melanoma or an abnormal mole phenotype (discussed later)—should benefit most from behavioral modification. Adults with numerous nevi should be examined for other melanoma risk factors, and observed appropriately (see later discussion).

Dysplastic Nevi

Origin of the Concept and Current Controversy

Moles with an unusual structure (Table 3) were first noted in families with a high incidence of melanoma. These were first reported as the "B-K mole syndrome" to acknowledge families "B" and "K"[68] and as the familial atypical mole and melanoma (FAMM) syndrome.[69] Shortly thereafter, these mole patterns were described in patients with and without melanoma who lacked a family history of melanoma, and the concept of the dysplastic nevus syndrome was expanded to include a "sporadic" dysplastic nevus syndrome for nonfamilial cases.[70] Controversy then began when the clinical definition was extended so that the presence of smaller lesions and fewer

TABLE 3.—*Clinical Features of Typical Nevi, Atypical Nevi, and Melanoma*

Clinical Feature	Camman Nevi	Atypical Nevi	Melanama
Size	Usually <5 mm	Varies, often >5 mm	Varies, may be >10-15 mm
Shape	Round; well-defined borders	Irregular; ill-defined borders	Irregular; notched borders
Color	Even	Variable; shades of brown; may be very dark regions; erythema often present	Variable; shades of brown to black; also red (inflammation), white (regression), and blue (pigment deep in dermis)

moles was being diagnosed as the dysplastic nevus syndrome. About a third of patients in a referral melanoma clinic were found to have clinically dysplastic nevi,[70] whereas the prevalence of dysplastic nevi in the general population reported over the next few years ranged from 4.9%[71] to 49%.[72]

At the same time, controversy also grew over the histopathologic correlation with these atypical nevi. Both architectural changes—lateral extension of the junctional component beyond the central nevus, complex lentiginous elongation of the epidermal ridge pattern, and fibroplasia of the papillary dermis—and cytologically noted atypia were included in the original definition. These changes also occur along a spectrum, and controversy similarly arose about the defining limits. Some pathologists required microscopic evidence of atypia of melanocytes in their definition of dysplasia.[73,74] In a review of early and nonfamilial cases, dysplastic nevi were divided histologically into low-grade and severe, based primarily on the degree of atypia of the junctional melanocytes.[75] Other authors accepted either architectural or cytologic changes.[72] Conversely, one author has categorically rejected both the clinical and histologic spectrums of dysplastic nevi on the grounds that dysplastic nevi should be considered merely melanocytic nevi of a flat and common type.[76] At the most recent National Institutes of Health consensus conference on the subject,[3] it was recommended that the clinical term "atypical nevus" be substituted for "dysplastic nevus" and that a more cumbersome description of architectural changes and cytologic atypia for the histologic dysplastic lesion be adopted. Nonetheless, the biologic concept of melanocytic dysplasia is useful in understanding the spectrum of tumor progression.[77]

Familial Atypical Mole or Melanoma Syndrome

Despite the foregoing controversy concerning the definition of melanocytic dysplasia, the existence of a syndrome of familial melanoma, defined as kindreds having two or more first-degree relatives with melanoma and in which nearly all affected persons have an unusual mole pattern that is characterized by an increased number of clinically atypical nevi (see Table 3), is noncontroversial.[3] Variably called the familial atypical multiple mole or melanoma (FAMM) syndrome,[78] the familial dysplastic nevus syndrome, type D2,[79] or the B-K mole syndrome,[68] the disorder is inherited as an autosomal dominant trait with incomplete penetrance and variable expressivity.[15,78,80-82] Linkage studies have suggested a locus on chromosome 1p,[83] but this has been refuted in other kindreds.[82,84-86] More recently, linkage to a cancer-associated region was demonstrated on the short arm of chromosome 9.[87] Whether these differences in linkage analysis are due to the use in some studies of an ambiguous marker, the "dysplastic" nevus, rather than melanoma, as suggested by some authors,[84,87] or reflect genetic heterogeneity is unclear. The latter interpretation is favored by evidence of clinical heterogeneity, including familial melanoma kindreds without dysplastic nevi,[82,86] or with ocular melanoma or other malignant neoplasms.[88,89] Affected family members can be identified in childhood or adolescence by the appearance of multiple nevi having the clinical (see Table 3) or histopathologic features of atypical or dysplastic nevi. It has been estimated that affected persons in FAMM kindreds have a 100% risk of a melanoma developing by age 70.[15,79] Melanomas develop at an earlier age in FAMM kindreds than in the general public,[78] and survivors are at high risk for additional primary melanomas.[15] Close surveillance of these patients for the detection of early melanoma is clearly warranted.[3]

Melanoma Risk Associated With Atypical ('Dysplastic') Moles

Whereas the presence of atypical moles, characterized by irregularities of pigmentation and shape, often with hazy borders and large size (see Table 3), is a strong predictor of melanoma risk in familial melanoma kindreds,[15] the importance of atypical moles in the general public is controversial.[3] Nonetheless, several studies have shown an increased risk for melanoma associated with clinically defined atypical nevi (Table 4).[10,16-18,44,51] These studies compared mole phenotypes in a group of melanoma patients with those of an age- and usually sex-matched control (white) group. The precise definition of an atypical

TABLE 4.—*Melanoma Risk Associated With Clinically Defined 'Dysplastic' Nevi in Melanoma Patients versus Controls*

Study	Country	Definition	≥1 Dysplastic Nevi, %		Relative Risk
			Melanoma Patients	Controls	
Roush et al, 1986[10]; Nordlund et al, 1985[16]	Australia	>5 mm, irregular border, and haphazard pigmentation	34	7	7.7
Mackie et al, 1985[51]	Scotland	>5 mm and irregular borders, irregular pigmentation, or inflammation	38	20	2.1-4.5*
Holly et al, 1987[44]	United States	At least 3 of 6 criteria: ill-defined border, irregular border, irregular pigmentation, >5 mm, erythema, accentuated skin markings	55	17	3.8-6.3†
Halpern et al, 1991[17]	United States	>4 mm, macular component, variegation of color, and irregular or indistinct border	39	7	8.8
Garbe et al, 1989[18]	Germany	At least 3 of 5 criteria: >5 mm, irregular margins, ill-defined border, color variation, macular and papular components	45	5	7

*Relative risks for 1 or 2 atypical nevi: 2.1; for 3 or more atypical nevi: 4.5.
†Relative risks for 1 to 5 atypical nevi: 3.8; for 6 or more atypical nevi: 6.3

nevus varied among the studies, which may account in part for the variation in estimated frequencies of atypical nevi in both control groups and patients. In all studies, estimated relative risks were adjusted for other known melanoma risk factors, such as total number of melanocytic nevi, skin type, and sun exposures. Some studies showed that a greater number of atypical nevi conferred a higher relative risk of melanoma,[16,44,51] whereas in others no increment in risk was observed.[17,18] Patients with dysplastic nevi had higher total mole counts in both melanoma patients and control groups than did persons without dysplastic nevi.[44] Moreover, patients with higher mole counts also had a greater number of atypical nevi.[44] Thus, although high numbers of moles and atypical moles are statistically independent risk factors for melanoma, they commonly occur in the same person. Hence, a strong correlation of melanoma risk with "nevus density" has been shown in which both the number and size of nevi are considered.[90]

The term "atypical mole syndrome" has been proposed to encompass the phenotype of an increased number of nevi (more than 100), some of which are large (>8 mm) and have atypical features.[91] Prospective follow-up of patients with this phenotype has shown a high risk for melanoma[92]; that is, over an average follow-up of four years, melanoma developed in 4.8% of these patients (in comparison with about a 1% risk of melanoma developing from ages 0 to 75 in the general population). The subset at greatest risk for melanoma comprised patients with the atypical mole syndrome and a previous melanoma. Although this study may reflect the bias of a referral center, a similarly high risk of melanoma associated with an abnormal mole phenotype was observed in a prospective study of nonreferred patients.[93]

Abnormal Mole Phenotypes and Melanoma Risk

The foregoing studies provide strong support for a clinically defined abnormal mole phenotype (Table 5) in which both the number of nevi and their quality (banal or atypical) are considered. Persons with an unquestionably abnormal mole phenotype form a relatively small fraction of the population and yet carry a greatly increased risk for melanoma.[93] Clearly a continuum of mole patterns exists from persons with few to no moles, to those with a moderate number (25 to 50) of nevi and some with possible to probable atypical features, to those with many moles (>50) and several to many that are clearly atypical.[93] It will be difficult, therefore, to rigidly define phenotypes and to defend these definitions.

TABLE 5.—*Mole Patterns*

Male Feature	*Normal Male Pattern*	*Abnormal Male Phenotype*
Number	None to few (<25)	Many (>50)
Size	<5 mm	Variable: small to large, often several >5 mm
Color and shape	Uniform pigmentation, well circumscribed	Some to many nevi with irregular pigmentation, ill-defined borders, or erythema

TABLE 6.—*Follow-up of Patients With an Abnormal Mole Phenotype*

Male Pattern	*Other Risk Factors*	*Nevus Photography*	*Follow-up Intervals, mo*
Abnormal	FAMM kindred: previous melanoma	Yes	3-4
Abnormal	FAMM kindred: no previous melanoma	Yes	4-6
Abnormal	Previous melanoma	Yes	4-6
Abnormal	Immunosuppressed	Yes	4-6
Abnormal	None	Yes*	12
Possibly abnormal	Actinic damaged skin	Yes*	12
Normal	FAMM kindred: no previous melanoma	No	12

FAMM = familial atypical mole or melanoma

*If photography services are readily available.

The diagnosis of an abnormal mole pattern is one of gestalt, best achieved by standing back from the patient and taking in the whole picture. As a working definition, persons either with many nevi (>100) with or without atypical nevi, or with many nevi (>50) and with one or several clinically atypical nevi, should be considered to have an abnormal mole phenotype. Such patients should be examined closely for melanoma and any lesions suspicious for melanoma excised. The tendency to form atypical nevi, even outside FAMM kindreds, is familial.[94] First-degree relatives of patients with an abnormal mole phenotype should therefore be examined.[95,96]

To prescribe a plan for follow-up care, the presence of other known melanoma risk factors should be ascertained, particularly a personal or family history of melanoma, the presence of immunosuppression, and signs of pronounced sun sensitivity or excessive sun exposures (Table 6). Certain genetic disorders confer an exceedingly high risk for melanoma, such as xeroderma pigmentosum,[12] and members of FAMM kindreds who have already had one melanoma.[79] Close surveillance—every three to four months—of these patients is warranted. Members of FAMM kindreds with abnormal mole phenotypes in whom a melanoma has not yet developed should also be observed closely—every three to six months. Similar follow-up intervals are recommended for persons with an abnormal mole phenotype and either a previous melanoma or immunosuppression. Other patients with an abnormal mole phenotype may be observed annually. Because of the occasional discordance of atypical nevi and melanomas in FAMM kindreds,[15] adult members with a normal mole pattern should also be examined annually.

In general, we recommend excisional biopsy only of nevi whose clinical features are suspicious for melanoma (see Table 3). Often the melanoma will stand out from its neighbors in a field of common and atypical nevi as the "funniest" or "ugliest" mole (Figure 1). When patients are seen for the first time with numerous and varied atypical nevi, excisional biopsy of one or two of the most atypical

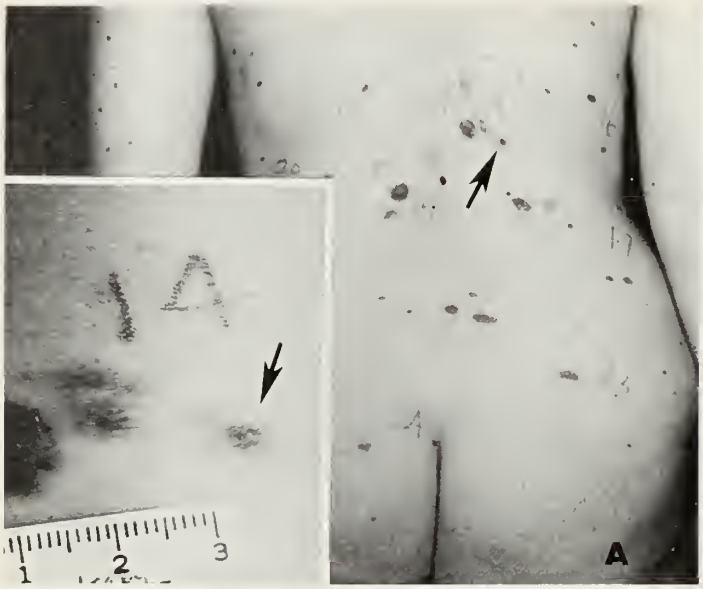

Figure 1.—**A,** The lower back and buttocks of a 28-year-old woman with an abnormal mole pattern are shown. The numbers refer to a map of close-up prints. The inset shows a close-up of a group of atypical nevi, including a precursor lesion **(arrow). B,** The patient returned after being lost to follow-up for 2 years and reported that several nevi had enlarged during a recent pregnancy. The lesion **(arrow)** is larger and much darker. It now shows pigment irregularity and notched borders that are suspicious for melanoma. An in situ melanoma was found on excisional biopsy of this lesion.

nevi to exclude early melanoma may be reasonable. New or changing pigmented lesions as a general rule should be removed, although there are reasonable exceptions. For example, new or enlarging nevi in adolescents and young adults (younger than 30 years) are common and need only be removed if they have suspicious features.

The role of photographic documentation in observing patients with atypical nevi has been controversial.[97,98] The major obstacle to recommending universal implementation of nevus photography in the follow-up of high-risk patients is the limited availability of services providing high-quality, standardized views. We and others have found photographs useful in observing adults with an abnormal mole phenotype (see Figure 1).[15,99,100] Their usefulness in detecting early melanomas in high-risk patients has been demonstrated by the New York University Skin and Cancer Unit.[92,101] In their experience, 60% of melanomas were detected solely on the basis of a change in the photographic record. Moreover, about 60% of malignant neoplasms arose de novo, that is, they were not associated histopathologically with a preexisting nevus. This implies that removing all clinically atypical nevi is not warranted even in high-risk patients because, in addition to the impracticality of removing what are often many lesions, such efforts will not eliminate risk. It may be prudent, however, to consider removing nevi in locations that are difficult to photograph and observe, such as the scalp, in high-risk persons, such as affected members of FAMM kindreds.[102] In the future, newer technologies, including epiluminescence microscopy (dermatoscopy) and digitalized images, may facilitate the follow-up of high-risk patients.[103,104]

Summary and Conclusions

In this review we have examined the factors that predispose persons to the development of melanoma, emphasizing the relationship between melanocytic nevi (moles) and melanoma risk. An understanding of the evolution of nevi in patients of different ages and the risks of melanoma associated with nevi of different types will be important to primary care physicians when addressing the concerns of their patients. Patients at varying degrees of risk may express concerns about their nevi. Some may have had family members or friends with melanoma, perhaps with a rapidly fatal outcome, and they may worry about either specific moles or their moles in general. Parents worry about their children, and spouses worry about each other. In our experience, many patients are reassured by our counseling, as most have imagined the risk of melanoma to be greater than we have counseled. In a recent study of the relative frequency of diagnoses in pigmented lesions removed and sent to a group of pathology laboratories,[105] of almost 3,000 consecutive examinations, 71% were benign nevi, 22% were diagnosed as "dysplastic," and preinvasive or invasive melanoma each accounted for less than 1% of such lesions. These data can help to reassure patients who are having biopsies done or who have moles that are being observed. These figures also suggest

that physicians are removing a high percentage of benign nevi in an attempt to diagnose early melanoma.

In most instances, follow-up of high-risk patients by physicians thoroughly trained in the diagnosis of pigmented lesions, such as dermatologists, is indicated (see Table 6). But the recognition of abnormal mole patterns for appropriate patient referrals is an important task for primary care physicians. In addition, all physicians should be familiar with the clinical signs of melanoma[1,80,106] to facilitate the early diagnosis and treatment of these epidemic cancers in their patients and family members. In this time of change in the health care system, the responsibility for the initial recognition of early melanoma will increasingly fall on primary care physicians. Our intent with this review is to provide some of the background information required in this role.

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Hormonal Therapy for Stage D Cancer of the Prostate

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Adenocarcinoma of the prostate is the most common malignant neoplasm occurring in men. About half of patients present with metastatic disease. The mainstay of the treatment of stage D cancer of the prostate is hormonal therapy. Bilateral simple orchiectomy remains the gold standard with which other therapies must be compared. Luteinizing hormone-releasing hormone analogues and antiandrogens are now most commonly used but are costly. Initiating hormonal therapy immediately on diagnosing metastatic disease appears to have some advantage over delaying therapy until a patient is symptomatic. Total androgen blockade also appears to be beneficial in terms of survival but at high cost.

(Gudziak MR, Smith AY: Hormonal therapy for stage D cancer of the prostate. West J Med 1994; 160:351-359)

Adenocarcinoma of the prostate, the most common malignant tumor occurring in men, was newly diagnosed in 165,000 men in 1993.[1]* As the second leading cause of death from cancer in men, it accounts for 35,000 deaths per year.[1] Half of patients may have metastatic or stage D disease (Table 1)[2,3] at diagnosis. Fortunately, more than 80% of these patients will respond symptomatically to hormonal therapy.[4] The androgen sensitivity of prostate cancer and the tumor regression that follows bilateral orchiectomy was first recognized by Huggins and Hodges in 1941, establishing "androgen deprivation" as the mainstay of therapy for advanced prostate cancer (Table 2).[5]

Despite hormonal therapy, androgen insensitivity eventually develops in nearly all patients with advanced prostate cancers. More than 85% of patients with stage D1 disease will have progression of their disease within five years.[6,7] Patients with stage D2 disease have a median survival of only 30 months and a five-year survival of 20%.[6,7] Progression to stage D3 disease with the development of androgen insensitivity usually occurs 12 to 16 months after endocrine therapy is initiated.[6,7] Following progression after hormonal therapy, half of patients die within six months of relapse.[8,9] The mean survival of patients presenting with metastatic disease is 1.8 years.[9]

The criteria for initiating hormonal therapy for prostate cancer have included the presence of metastatic disease, localized disease in older men not candidates for surgical or radiation therapy, and recurrence after surgical or radiation therapy. Numerous prognostic factors have been identified that favorably affect progression-free survival after the initiation of hormonal therapy. These have included performance status according to criteria established by the Eastern Cooperative Oncology Group (ECOG)[10-12]; the extent of disease by bone scan[13,14]; an acid phosphatase level less than two times normal[13]; an alkaline phosphatase level of less than 115 U per liter[11,15]; pain before the initiation of therapy[11]; a serum testosterone level of greater than 250 nmol per liter[11,16]; and tumor size.[13] Three studies that used multivariate analyses found ECOG performance status to be the most predictive of response and median time to failure.[11,12,15]

Androgen Production

The production of androgens in humans is mediated through the hypothalamic-pituitary-testicular axis (Figure 1). The hypothalamus detects decreased serum testosterone and secretes luteinizing hormone-releasing hormone (LH-RH) that migrates to the anterior pituitary through the hypophyseal portal system of veins. Under the stimulation of LH-RH, the anterior pituitary gland secretes luteinizing hormone. Luteinizing hormone release stimulates androgen production by Leydig cells located in the interstitium of the testes. The testes secrete primarily testosterone, but other steroids are secreted in smaller quantities such as dihydrotestosterone, androsterone, androstenedione, progesterone, and 17-hydroxyprogesterone. Testosterone circulates largely bound to serum proteins including albumin (54%) and testosterone-binding globulin (44%). Only the unbound fraction is active. Testosterone is converted in the prostate to dihydrotestosterone, a more potent androgen, by the enzyme 5α-reductase. Only a small portion of dihydrotestosterone is produced directly by the testes. High circulating levels of testosterone, as well as estrogen, inhibit the release of both luteinizing hormone by the pituitary and LH-RH by the hypothalamus.

The adrenal gland is a source of weak androgens such

*See also the editorial by F. V. Mayer, MD, "Future Trends in the Incidence and Management of Prostate Cancer," on pages 380-381 of this issue.

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ABBREVIATIONS USED IN TEXT

DES = diethylstilbestrol
ECOG = Eastern Cooperative Oncology Group
FSH = follicle-stimulating hormone
LH-RH = luteinizing hormone-releasing hormone
PSA = prostate-specific antigen
VACURG = Veterans Administration Cooperative Urological Research Group

as androstenedione and dehydroepiandrosterone, which together account for 10% or more of circulating androgens and are not under the direct control of luteinizing hormone.

Surgical Castration

Since the benefits of androgen ablation were established in patients with advanced prostate cancer,[5] bilateral orchiectomy, which provides prompt castrate levels of testosterone (< 50 nmol per liter), remains the standard with which all other forms of therapy are compared.[17-19] The procedure has low morbidity and mortality.[17,20,21] Possible advantages of orchiectomy include lower cost (Table 3), rapid response, and therapeutic compliance. Serious side effects from orchiectomy include a loss of libido, impotence (100%), and mild to severe hot flashes.[22] Subcapsular orchiectomy may be more psychologically appealing to some patients. The procedure has been criticized because of the possibility of incomplete removal of functioning tissue; however, studies have shown that testosterone is reduced to castrate levels and remains so even after stimulation with human chorionic gonadotropin.[23,24]

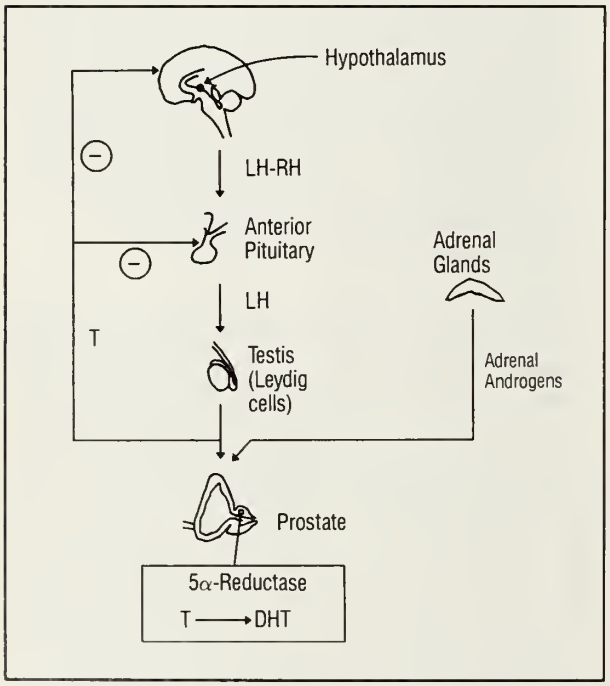

Figure 1.—The diagram shows the mechanism of the production of androgens through the hypophyseal-pituitary-gonadal axis. The hypothalamus secretes luteinizing hormone-releasing hormone (LH-RH) in a pulsatile manner, regulating the release of luteinizing hormone (LH) by the anterior pituitary gland. Luteinizing hormone then stimulates the secretion of testosterone (T) by Leydig cells in the testes. Testosterone is reversibly bound to albumin and testosterone-binding globulin so that only about 2% remains in the unbound active fraction. Testosterone in turn regulates LH-RH and LH by negative feedback (−). The adrenal glands also contribute androgens such as androstenedione and dehydroepiandrosterone under the control of corticotropin that is released from the anterior pituitary by stimulation from corticotropin-releasing factor and vasopressin from the posterior pituitary. Testosterone is converted to the more potent dihydrotestosterone (DHT) within the prostate by the enzyme 5α-reductase.

TABLE 1.—*Staging System for Patients With Stage D (Advanced) Prostate Cancer**

Prostatic Cancer Stage	*Clinical Criteria*
D0	Localized disease with a normal bone scan but serum acid phosphatase level elevated × 2
D1	Pelvic lymph node involvement
D2	Evidence of distant metastases in bone or other organs
D3	Relapse in the presence of D2 disease after adequate endocrine therapy

*From Whitmore,[2] modified by Jewett.[3]

Medical Castration

Estrogens

In the treatment of prostate cancer, estrogens function primarily by ablating the release of luteinizing hormone by the anterior pituitary gland and thereby removing the stimulation of testosterone production by the testes. Estrogens also increase the synthesis of testosterone-binding globulin by the liver, inhibit the functions of 5α-reductase, and inhibit dihydrotestosterone binding both to its receptor and to DNA polymerase. Evidence of a direct cytotoxic effect of estrogens on prostate cancer cells has been shown.[25-27]

Diethylstilbestrol (DES) has historically been the most commonly used estrogen in the treatment of prostate cancer. A dose of DES, 3 mg orally daily, provides castrate levels of testosterone in 7 to 21 days.[22,28] Even 1 mg per day may achieve castrate levels of serum testosterone in most but not all patients.[29] In the first Veterans Administration Cooperative Urological Research Group study (VACURG I), patients taking 5 mg of DES had increased cardiovascular complications compared with controls. The second study, VACURG II, showed that administering this hormone in a dosage of 1 mg per day was as effective as giving 5 mg per day with fewer cardiovascular side effects, although castrate levels of testosterone were not consistently obtained.[31,32] Complications of DES therapy include salt and water retention, gynecomastia and breast tenderness, nausea and vomiting, thromboembolic events—reported to be 300% higher than in age-matched populations[33]—loss of libido, impotence, and an increased incidence of cardiovascular disease. Although DES is inexpensive (see Table 3) and its use obviates the need for an operation, it is now used less frequently due to improved toxicity profiles of newer drugs. Estramustine, an estrogenic agent combined with a nitrogen mustard moi-

TABLE 2.—*Endocrine Therapies for Prostate Cancer*

Therapy	*Type*
Surgical castration	Bilateral simple orchiectomy, bilateral subcapsular orchiectomy
Medical castration	Estrogens: diethylstilbestrol; LH-RH agonists or antagonists: leuprolide acetate, goserelin, buserelin
Antiandrogens	Androgen receptor antagonists: flutamide, nilutamide, casodex; 5α-reductase inhibitors: finasteride; steroidal antiandrogens: megestrol acetate, cyproterone acetate
Adrenal suppression	Surgical adrenalectomy; medical adrenalectomy: ketoconazole, aminoglutethimide
Direct cytotoxic effect	Stilbestrol diphosphate

LH-RH = luteinizing hormone-releasing hormone

ety to provide specific cell toxicity, was shown to have no advantage over DES for primary therapy.[34]

Luteinizing Hormone-Releasing Hormone Agonists or Antagonists

The LH-RH analogues have an amino acid substitution glycine 6 with leucine and deletion of a terminal amino amide group that gives them a higher affinity for LH-RH receptors in the anterior pituitary than does native LH-RH.[35] Administering a bolus of an LH-RH analogue causes a release of luteinizing hormone and an increase in testosterone production called the "flare" phenomenon.[36] Long-term administration of LH-RH analogues disrupts the pulsatile release of gonadotropin-releasing hormone with an inhibition of LH-RH receptors that paradoxically causes gonadotropin suppression.[35] Serum testosterone levels reach castrate levels within four weeks of starting treatment in 90% of men.[37] Luteinizing hormone-releasing hormone analogues maintain plasma testosterone levels in the castrate range for the duration of therapy.[38]

Several studies have examined the efficacy of LH-RH analogues versus DES or orchiectomy. The Leuprolide Study Group randomly assigned 199 previously untreated patients with metastatic prostate cancer to receive either subcutaneous leuprolide acetate, 1 mg per day, or DES, 3 mg per day.[39] Time to progression was similar in the two groups, with no significant difference in one-year survival (87% for leuprolide versus 78% for DES treatment). Fewer cardiovascular complications and less gynecomastia occurred in the leuprolide-treated cohort. A randomized trial comparing the use of the LH-RH analogue buserelin with that of DES or orchiectomy in 160 patients with stage D2 disease showed no notable differences between treatment groups for progression-free survival, best response, or overall survival.[40] The treatment efficiency of the LH-RH analogue is equivalent to that of either DES or orchiectomy.[37,40] No one analogue has proved superior to another.[41] Major side effects of treatment with LH-RH analogues include hot flashes (an incidence as high as 72%),[13,37] gynecomastia (12% to 16%),[13,37,38] irritation at the injection site (12%),[37] and the flare phenomenon.

The initial stimulation of testosterone production by the increased release of luteinizing hormone may be associated with increased bone pain four to ten days after starting a regimen of an LH-RH analogue. This flare phenomenon usually resolves spontaneously. In patients who have spinal metastases and particularly those with lower extremity motor deficits, the use of LH-RH analogues is contraindicated because spinal cord compression may occur during the flare, leading to paralysis. Impending ureteral obstruction is also a contraindication to the use of LH-RH analogues alone. Antiandrogens such as flutamide or DES have been used effectively to block the flare phenomenon in the first two weeks of LH-RH analogue therapy.[42,43]

The two LH-RH analogues that are approved by the United States Food and Drug Administration include leuprolide acetate and goserelin. Both are available in depot preparations that require once-a-month injections: Lupron Depot (TAP Pharmaceuticals) and Zoladex (ICI Americas), respectively. Depot preparations have been shown to be as effective as once-a-day administration.[36] Lupron Depot is administered intramuscularly, and Zoladex is deposited as a pellet through a 14-gauge needle subcutaneously. Monthly administration improves patient acceptance and compliance but is expensive (see Table 3).

Antiandrogens

Flutamide. Flutamide is a nonsteroidal anilide and a potent antiandrogen. Administered as an oral dose of 250 mg three times a day, flutamide appears to inhibit the uptake and binding of testosterone and dihydrotestosterone to nuclear receptors, producing a secondary increase in serum testosterone levels.[44-46] Because serum testosterone levels are maintained, a major advantage of flutamide and other nonsteroidal antiandrogens used as monotherapy is the preservation of potency. Flutamide has been more commonly used in combination therapy to achieve total androgen blockade (see Total Androgen Blockade).

In one study, 73 previously untreated patients with stage D prostate cancer were given flutamide monotherapy.[47] Most patients (85%) had a favorable response lasting 2 to 56 months (mean 12.5 months) as determined by a decreased prostatic acid phosphatase level, a decreased number of bony metastases, decreased bladder outlet obstruction, and a decrease in prostate size and pain. Sexual potency was preserved in 86% of patients. Several randomized prospective trials show that using flutamide alone is as effective as DES in the treatment of advanced prostate cancer.[48-50] In one small randomized trial, the use of flutamide, 750 mg per day, was compared with that of DES, 3 mg per day.[49] An objective response or stabilization of disease was seen in 13 of 20 patients receiving flutamide and 8 of 20 patients who received DES. Whereas

TABLE 3.—*Cost of Hormonal Treatment of Stage D Prostate Cancer*

Therapy	*Cost Item*	*Cost/Item or Cost/Month, $**	*Cost for 2 Years of Therapy, $*
Bilateral orchiectomy	Surgeon fee	765	
	Hospital or other	1,193	
	Total	2,695	2,695
Diethylstilbestrol, 3 mg orally daily	1-mg tab	8	192†
Flutamide, 250 mg orally 3×/day	125 mg tab	299	7,176
Leuprolide acetate (Lupron Depot)	7.5 mg/ml	415	9,960
Goserelin (Zoladex), 3.6 mg subcutaneously every 28 days	3.6 mg pellet	322	7,728

*Reflects the average of 2 hospital or pharmacy estimates from the Albuquerque, New Mexico, area, based on June 1991 fees.

†Cost does not include excess cardiovascular morbidity for about 10% of patients, which has been estimated to add $1,600 to $2,000 per year to cost estimate for average patient (C. A. Olsson, "Cost of Diethylstilbestrol Underestimated," *AUA* [American Urological Association] *Today*, 1993 Feb; 6:3).

no substantial loss of libido or potency was noted with flutamide therapy, all of the patients receiving DES became impotent. Recent reports have suggested that flutamide may function as an agonist in patients treated with total androgen blockade. Prostate-specific antigen (PSA) levels declined, and clinical improvement was noted in several patients with apparent stage D3 prostate cancer when flutamide use was discontinued.[51] The main disadvantage of flutamide therapy is cost (see Table 3). Major side effects include gynecomastia (25% to 50%), severe diarrhea (10% to 15%), flushing (15% to 30%), and liver function abnormalities.[52]

Nilutamide. Nilutamide (Anandron) is an equipotent nonsteroidal antiandrogen with similar efficacy to flutamide as monotherapy; it is usually used in combination with medical or surgical castration.[53,54] Nilutamide has improved pharmacokinetics over flutamide, allowing doses of 300 mg per day. A recent prospective, randomized trial compared nilutamide with orchiectomy (n = 225) versus orchiectomy and placebo (n = 232). Significantly longer progression-free survival occurred for the nilutamide-treated group (20.8 months versus 14.9 months, ($P \leq .005$). Overall survival was not significantly different ($P \leq .07$).[55] The side effects of nilutamide are similar to those of flutamide, but also include brief impairment of adaptation to dark (an incidence as high as 90%) and interstitial pneumonitis (1% to 3%).[56]

Casodex. Casodex, a new nonsteroidal pure antiandrogen, is currently undergoing Phase II and III trials. The drug competes with dihydrotestosterone for binding to the androgen receptor. The response of patients with stage D prostate cancer to antiandrogens has been similar to that seen with conventional hormonal therapy.[48-50] No convincing benefit has been shown for patients with hormone-refractory disease.[57]

5α-Reductase Inhibitors

Finasteride. This drug, a 5α-reductase inhibitor currently undergoing trials in Europe, acts to inhibit the conversion of testosterone to dihydrotestosterone in target cells. Side effects with the use of this drug have been minimal, and it only rarely interferes with sexual function. Tissue testosterone levels are elevated dramatically, and thus far early clinical experience with finasteride for the treatment of prostate cancer has been disappointing. In a multicenter, randomized, placebo-controlled study of untreated patients with stage D prostate cancer, only PSA levels showed a small decrease, with no change in prostatic acid phosphatase levels, serum testosterone levels, prostate size, or bone scan appearance.[58]

Steroidal (Mixed) Antiandrogens

Cyproterone acetate. Cyproterone acetate is a synthetic steroid with progestational activity. Although not approved for use in the United States, it has been used in Europe. Cyproterone acetate competes with testosterone and dihydrotestosterone for androgen receptors in the prostate, secondarily produces suppression of luteinizing hormone release, and inhibits dihydrotestosterone uptake into the nucleus.[59,60] Cyproterone acetate has also been reported to have cortisol-like action and to suppress corticotropin-adrenal function.[61] A large multicenter, randomized trial compared the intramuscular administration of cyproterone acetate, 300 mg per week, with that of estradiol, 100 mg per week.[62] Of 91 patients receiving cyproterone acetate, 83 (91%) had improved performance status versus 95% in the estrogen-treated cohorts. Side effects occurred in only 37% of patients treated with cyproterone acetate versus 94% of those treated with estrogen. A European randomized Phase III trial (European Organization for Research on Treatment of Cancer) of 210 patients compared the use of cyproterone acetate, 250 mg per day orally; medroxyprogesterone acetate, 500 mg intramuscularly three times per week for eight weeks and then 220 mg per day orally; and DES, 3 mg per day orally.[63] The five-year survival was 38% for DES, 32% for cyproterone acetate, and 14% for medroxyprogesterone acetate. Cardiovascular toxicity was 35% for DES, 19% for medroxyprogesterone acetate, and 10% for cyproterone acetate.[63]

Cyproterone acetate has also been used to block the flare phenomenon of LH-RH agonists.[64] Flare was successfully blocked in 23 patients treated with buserelin and cyproterone acetate, 150 mg per day orally.[65] But a randomized study of 71 patients with metastatic cancer that compared the use of an LH-RH agonist with an LH-RH

agonist plus cyproterone acetate showed no significant difference in progression rates (38% versus 41%, respectively) once the flare period had passed.[66] For stage D3 disease, 15 patients were treated with cyproterone acetate, 200 or 250 mg per day orally.[67] Pain abated in four of ten and voiding symptoms in one of four. Similar results with pain relief were noted in 12 of 19 patients and increased energy in 5 of 13.[59]

An important aspect of cyproterone acetate therapy is its reversibility, with the return of serum testosterone levels to normal after therapy is stopped.[68] Cyproterone acetate has also been reported to lose effectiveness with long-term use.[69] Cardiovascular side effects may occur in 10% to 15% of patients[63,68,70] and gynecomastia in 13%.[62] Several studies have shown mild serum prolactin elevations to the upper limits of normal with the use of cyproterone acetate.[68,71] In short, this drug provides excellent androgen deprivation, even in monotherapy, with minimal cardiovascular toxicity.

Megestrol acetate. A regimen of megestrol acetate (Megace), 80 to 100 mg per day, will reduce testosterone levels to just above castrate levels in one month with a concomitant decrease in levels of luteinizing hormone and follicle-stimulating hormone (FSH). With administration for as long as four to six months, however, megestrol loses some of its activity, and serum levels of testosterone, luteinizing hormone, and FSH rise but not back to normal levels.[72] Adrenal androgens, androstenedione, and dehydroepiandrosterone sulfate are also suppressed.[73] The antiandrogenic qualities of megestrol acetate are limited.[73]

Megestrol acetate, 120 mg per day intramuscularly, has been combined with low-dose DES, 0.1 mg per day orally. This provides a sustained decrease of testosterone to castrate levels and a blockade of adrenal androgens with fewer DES-related side effects. When 23 patients with stage D2 prostate cancer using this regimen were compared with 23 patients treated with castration or DES, 1.0 to 3.0 mg per day, the median time to progression was found to be similar but slightly favored the use of DES plus megestrol—21 versus 16 months.[73] A regimen of DES, 3 mg per day, was compared with that of megestrol acetate plus DES, 0.1 mg per day. There were no differences in time to progression or survival, but less toxicity was seen with the use of megestrol and low-dose estrogen.[74] Even at very low doses, however, when combined with megestrol, estrogen can cause edema and gynecomastia.[75] Megestrol is not appropriate for monotherapy, but in combination with low-dose estrogens may be another regimen for achieving total androgen blockade.

Adrenal Suppression

Bilateral adrenalectomy was performed in 1945 by Huggins and Scott in four patients in whom initial hormonal therapy for prostate cancer had failed.[76] Due to a lack of glucocorticoid replacement, survival was less than 11 days in three patients. One patient survived 116 days. Minimal success was also reported in 1953.[77] With cortisol replacement, bilateral adrenalectomy became possible. In a review in 1973, objective responses were rare.[78] Thus, further efforts have been aimed at medical adrenalectomy.

Administering aminoglutethimide inhibits both testicular and adrenal steroidogenesis by blocking cytochrome P-450 hydroxylation of C21, C11, and C18 steroids and the conversion of cholesterol to pregnenolone.[79] Glucocorticoid replacement is necessary with treatment. Aminoglutethimide has been used primarily as a second-line treatment in patients who have progression of disease after standard endocrine therapy (stage D3).[31]

Ketoconazole administration also inhibits the synthesis of both testicular and adrenal androgens by blocking the cytochrome P-450 of C14 to 20 lyase, 17 to 20 desmolase, and 12-hydroxylase.[80] Ketoconazole has also been used as a second-line drug in patients for whom initial hormone therapy has failed. In addition, it is used when a rapid reduction in serum testosterone levels is necessary, such as for patients presenting with disseminated intravascular coagulation or impending spinal cord compression in whom orchiectomy is not possible. Ketoconazole therapy at 400 mg administered orally every eight hours will reduce serum testosterone levels to castrate levels in 24 hours.[81] The effect of ketoconazole is reversible after therapy is stopped. Complications of ketoconazole therapy may include severe hepatitis (1 per 16,000, usually reversible), a loss of libido, weakness or lethargy, and glucocorticoid deficiency.[82-84] Ketoconazole has also been used empirically, as initial therapy or in combination with LH-RH analogues.[84] Ketoconazole is not effective for hormone-refractory disease, however.[82]

Direct Cytotoxic Effect

In the treatment of prostatic cancer, low-dose estrogens exert their effect through the pituitary-gonadal axis. High-dose estrogens have a direct cytotoxic effect. Diethylstilbestrol has been shown to have inhibitory effects on DNA and RNA synthesis in both benign and malignant prostatic tissue.[85] It inhibits RNA polymerase activity in prostate tissue.[86] Stilbestrol diphosphate, a biologically inactive estrogen, when administered intravenously is converted by acid phosphatases to DES. Because stilbestrol diphosphate is water soluble, it can be administered in high doses.[25] Protein synthesis is inhibited in prostatic carcinoma cells isolated from culture by DES concentrations of 1 to 5 μg per ml.[26] Concentrations of DES of 25 μg per 10 grams of prostate tissue were found in prostatectomy specimens 30 minutes after stilbestrol diphosphate was administered intravenously.[87] Clinical evidence has also shown intravenous stilbestrol diphosphate to be effective in hormone-refractory prostate cancer. A beneficial effect of high-dose stilbestrol in 34 patients refractory to a standard oral dose of DES was first reported in 1955.[88] With the intravenous administration of 250 to 1,250 mg of stilbestrol diphosphate over 20 minutes daily, 26 patients (76%) had subjective responses, but only 3 (9%) of these had objective responses.[88] In another study, 29 patients were given high doses of stilbestrol diphosphate; 22 (76%) had lessened bone pain, and 13 (45%) had a significant fall in PSA levels (44% to 93.4% of pretreatment levels).[25] Of

19 other patients with hormone-refractory disease who were treated, 11 (58%) showed improvement.[89] Stilbestrol diphosphate was given for seven to ten days as a slow intravenous push of 1,100 mg or by 20-minute infusion of the same dose in 200 ml of a saline solution.[90] Rapid administration can cause perineal pain, nausea and vomiting, and bone pain in patients with widespread bony metastases. Pulmonary embolism, myocardial infarction, cerebrovascular accidents, and deep venous thrombosis are rare if the course is limited to seven days. The duration of response for a seven-day course is 3.8 ± 1.6 months if the PSA level declines. With no decline, a subjective response lasts only two months.[25] Patients with hormone-refractory disease with severe bone pain, uremia, or spinal collapse should be considered for intravenous stilbestrol diphosphate treatment.

Total Androgen Blockade

The concept of total androgen blockade in endocrine therapy for prostate cancer was pioneered ten years ago. Patients treated with an LH-RH analogue (leuprolide acetate) who also received an antiandrogen (flutamide) showed improved survival over historical controls.[91] There is clinical evidence that adrenal androgens may play a minor role in prostate cancer.[92-94] Adrenal androgens, androstenedione and dehydroepiandrosterone, account for 5% to 10% of circulating androgens in men and may be converted to dihydrotestosterone.[95,96] Furthermore, conventional endocrine therapy decreases serum testosterone levels about 95%, whereas prostate dihydrotestosterone levels fall only 60%.[14] The use of antiandrogens was theorized to block this residual androgen production and lead to total androgen blockade. If hormonal therapy fails, adding an antiandrogen may benefit some patients. Initial data from nonrandomized studies in hormone-refractory patients showed a 40% response rate.[10,91,96]

The introduction of LH-RH analogues and antiandrogens promoted an interest in total androgen blockade as primary therapy. In 1985 the National Cancer Institute Intergroup Study compared the use of leuprolide plus flutamide with that of leuprolide plus placebo in a double-blind randomized trial involving 603 previously untreated patients with stage D2 prostate cancer.[13] The median time to progression was 16.5 months for the combined therapy group and 13.9 months for the monotherapy group ($P \leq .039$). Median survival was 35.6 and 28.3 months, respectively ($P \leq .04$). Mild diarrhea was more common in the combined therapy group. The incidence of other side effects of nausea and gynecomastia was similar for both groups. Patients with minimal disease and good performance status benefited more and had not yet reached median survival at the trial's conclusion. The combination therapy produced less flare. The five-year follow-up on this study showed that the patients with minimal disease had reached the median time to progression and survival.[97] In the patients receiving combination therapy, the median time to progression was 58.3 months and survival 61 months versus 19.1 months and 41.5 months in the matched group who received leuprolide plus placebo. Patients with minimal disease had a 20-month survival advantage with combination therapy.

These results have been disputed, however. In a series of experiments using the Dunning rat tumor model, rats receiving orchiectomy plus flutamide had tumor growth and survival rates that were no better than those of rats receiving orchiectomy alone.[98] A randomized trial of 327 European patients with locally advanced or metastatic prostate cancer compared the use of orchiectomy versus that of goserelin plus flutamide, 250 mg three times a day.[99] The median time for follow-up was 1.5 years, and the median duration of survival was approximately 2.5 years in both groups. The time to the first objective evidence of progression or subjectively noted progression was substantially better for those given goserelin plus flutamide, but no difference in overall survival was seen. In another study, the use of the LH-RH analogue buserelin with and without cyproterone acetate was compared. No superiority of total blockade over testicular suppression alone was seen.[66]

Finally, a recent study from the International Prostate Cancer Study Group compared the use of goserelin with flutamide with its use alone in a randomized prospective trial of 571 previously untreated patients with locally advanced or metastatic prostate cancer.[100] After a median follow-up of two years, there was no difference in subjective or objective response rates, interval to progression (combination therapy, 760 days versus monotherapy, 985 days), or survival (median survival of 34.9 months in each group). In addition, increased gastrointestinal and liver toxicity in the combination-therapy group resulted in 44 patients being withdrawn from the trial.

Results of these studies suggest that patients with good performance status and minimal disease derive the greatest benefit from total androgen blockade, and this subgroup of patients should be targeted for therapy. Cost issues (see Table 3) are a consideration. Studies that show benefit of orchiectomy combined with the use of an antiandrogen, eliminating the more costly LH-RH analogue from the regimen, are encouraging from this perspective.

Early Versus Late Therapy

The early initiation of hormonal therapy—before symptoms appear—after the diagnosis of prostate cancer versus delaying therapy until symptomatic disease supervenes is controversial. In the 1950s instituting hormonal therapy immediately was thought fundamental to improved survival of patients with prostate cancer. This approach of promptly starting hormonal therapy was based primarily on three studies that showed improved survival of patients treated with orchiectomy or DES versus controls from the 1930s.[9,101,102] In the mid-1960s, however, the Veterans Administration Cooperative Urological Research Group's first trial compared four treatments—placebo; bilateral orchiectomy; DES, 5 mg per day; and DES plus orchiectomy—in 1,764 patients with stages C and D disease.[103] Most patients in the placebo group whose disease progressed were begun on hormonal therapy (70% in stage C and 100% of stage D). Therefore, this trial allowed for a comparison of early-versus-delayed hormonal therapy. No

survival benefit was seen. The second trial, VACURG II, studied different doses of DES—placebo, 0.2 mg, 1 mg, and 5 mg.[32,33] Initial results showed similar survival among the treatment groups, implying that there was no difference between delayed (placebo) and early hormonal therapy. In a retrospective study, 100 untreated patients with stage C and D disease from the Johns Hopkins (Baltimore, Maryland) Tumor Registry from the prehormone era (1937 to 1940) were compared with 100 similar patients treated with hormonal therapy (1942 to 1943). The date of diagnosis rather than the timing of hormonal therapy was found to have the greatest effect on survival.[104]

On the other hand, in the early 1980s studies of animals showed a benefit with early hormonal therapy. Late-versus-early hormonal treatment with androgen ablation, chemotherapy, or both was evaluated in Dunning R-3327 rats with prostatic adenocarcinoma. Animals who received early therapy had improved survival.[105,106] In a series of nonrandomized trials of patients with stage D disease treated with pelvic lymphadenectomy, radical prostatectomy, and immediate adjuvant therapy, disease-free survival was improved, but not overall survival. Five- and ten-year disease-free progression rates were 84% and 80%, respectively, for the early orchiectomy group versus 48% and 38%, respectively, with delayed therapy.[107] Other reports showed improvement in time to progression but no notable survival benefit.[108,109] A retrospective review was done of 68 patients with stage D1 disease who had 60 months of follow-up. Of these, 30 underwent immediate hormonal therapy and 38 had delayed treatment until the onset of bone metastases. The median interval to the appearance of bone metastases was 43 months in the delayed-treatment group and 100 months in the early-treatment group. The median interval to death was 90 versus 150 months, respectively, which shows a trend toward improved survival but was not statistically significant.[110] In 1988 the VACURG II data were reanalyzed, revealing a survival benefit with early hormonal therapy but only in patients younger than 74 years, who had higher grade tumors (Gleason's sum 7).[111] A mathematical model had been used to show a benefit of early therapy for younger patients with higher grade tumors.[112]

A poor prognosis has been shown for patients with aneuploid tumors despite early hormonal therapy.[107,113] The clinical course of 62 patients with stage D1 cancer was retrospectively analyzed and the DNA ploidy of paraffin-embedded tissue retrospectively determined.[114] Patients with diploid tumors receiving early endocrine therapy had improved disease-free survival. Although the intergroup study was not specifically designed to look at early-versus-delayed therapy, patients with minimal and presumably earlier disease who had good performance status (according to the ECOG standards) had longer survival free of progression and an increased median length of survival than did patients with severe disease and poor performance status.[13]

A number of factors correlate with metastatic potential or progression to the androgen-insensitive state. These include a high histologic grade,[115] aneuploidy,[113,116,117] more than six areas of uptake on a bone scan,[118] a volume greater than 1 ml,[119] a rising Gleason score,[16] a serum testosterone level before initiating therapy of less than 300 mg per dl,[16,118] and amplified *ras* and *myc* oncogene expression.[120]

Summary

The mainstay of the treatment of advanced prostate cancer is hormonal therapy. Orchiectomy, if acceptable to the patient, is the treatment of choice in terms of cost and compliance for patients with advanced disease and poor performance status. Antiandrogens are the first-line drug for patients wishing to maintain potency. The early initiation of hormone therapy shows some promise. Combination therapy may offer substantial benefit to patients with minimal disease and good performance status but possibly at great expense. Once a tumor becomes refractory to hormone therapy, current therapeutics are of minimal benefit.

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Epitomes

Important Advances in Clinical Medicine

Dermatology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in dermatology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Nevi—An Update

NEVI AND THEIR RELATIONSHIP to malignant melanoma continue to be an important and controversial subject. Today in the United States, the risk of melanoma developing is 1 in 105. If the rate increase continues, it is estimated that by the year 2000, the risk will increase to about 1 person in 75. It is still uncommon in nonwhites. Several studies have shown that the risk for malignant melanoma developing is proportional to the number of melanocytic nevi present, even if these are clinically normal. The relative risk is about 1.6 for persons with 11 to 25 nevi, 4.4 for those with 26 to 50 nevi, and 5.4 for those having 51 to 100 nevi. Additional studies have shown a direct relationship between the number of nevi and ultraviolet light exposure. The number of melanocytic nevi seen in a group of Australian students with exposure to intense solar irradiation was ten times greater than the number reported in some other studies of children in areas of relatively low sunlight. Along with the fact that some 30% to 50% of malignant melanomas probably arise in direct association with nevi, these studies emphasize the importance of the sun's role in malignant melanoma. It is therefore imperative that photoprotection—sunscreen, appropriate clothing, limited exposure—be adopted at an early age if we are to stem the dramatic rise in the incidence of malignant melanoma. On an environmental level, ozone depletion as a cause of increased ultraviolet light exposure should continue to be a concern.

The National Institutes of Health Consensus Conference on the Diagnosis and Treatment of Early Malignant Melanoma (January 1992) recommended that atypical moles (atypical or dysplastic nevi) now be called nevi with architectural atypia, with a statement as to the presence and degree of melanocytic atypia. Because this is rather cumbersome terminology, it is unlikely to gain wide acceptance. Atypical moles have macular or papular components and irregular borders. They are usually larger than common nevi and show color variation ranging from tan to dark brown, often on a pink background. A definite relationship exists between the presence of atypical moles and malignant melanoma either as precursor lesions or, less likely, as cutaneous markers for melanoma. Although all patients with atypical moles are at some increased risk for melanoma developing, those with a few atypical moles without any family history of melanoma are at only slightly greater risk than the general population. For those persons with many atypical moles and a family history of atypical moles with accompanying melanomas, the lifetime risk may be as high as 100%. Therefore, clinicopathologic correlation is imperative to arrive at a prognosis for patients with atypical moles.

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Look Out for Latex

ALLERGIC REACTIONS TO natural latex rubber, manifested as contact urticaria or allergic contact dermatitis, are probably responsible for at least 10% of occupational skin allergies in industrialized countries. Latex is a substance produced by the laticifer cells in the phloem of the rubber tree, *Hevea brazilensis*. It is harvested by wounding the trees and collecting the dripping milky latex. Natural latex is processed into rubber by adding various chemicals that include accelerators (carbamates, mercaptobenzothiazole, thioureas, naphthylamines, and thiurams), antioxidants (*p*-phenylenediamine, butylated hydroxytoluene) emulsifiers, ultraviolet inhibitors (benzophenones, resor-

cinol, cinnamates), colorants, fragrances, and biocides. These chemicals augment vulcanization (the cross-linking process) and enhance the stability of latex for industrial applications.

In the health care setting, immunoglobulin (Ig) E-mediated contact urticaria and anaphylaxis to natural latex rubber have recently been noted as an expanding and possibly life-threatening problem. This condition characteristically presents clinically as pruritus and urticaria affecting skin directly in contact with latex rubber (most commonly rubber gloves). Anaphylactic shock has developed in sensitive patients after exposure to latex during the course of physical examinations and surgical procedures. Protein antigens have been isolated from latex that react specifically to IgE antibodies isolated from latex-sensitive persons. This condition is diagnosed in sensitive persons by producing a positive prick test at 30 minutes with latex antigen. Health care professionals should scrupulously avoid the use of latex products in patients who have a history of latex allergy.

In contrast to immediate hypersensitivity, latex-rubber allergic contact dermatitis presents as eczematous dermatitis and is most frequently caused by latex rubber additives. Sensitivity, paradoxically, seems to occur most frequently by using protective rubber garments (gloves, masks, and boots). This form of delayed hypersensitivity reaction is mediated by T cells and is diagnosed by applying the offending chemical as a patch test that is examined after 48 hours and a second time three to seven days later.

Health care workers have an extraordinarily high incidence of rubber sensitivity, especially contact urticaria (estimates vary from 7% to 20%). The immediate treatment of patients with acute allergic sensitivities is the use of oral antihistamines. Allergic contact dermatitis to latex rubber can be controlled with the use of topical or parenteral steroids. People who are rubber sensitive must avoid products that contain latex antigen or the offending sensitizing additives. In the case of health care workers, this may require the use of gloves made of a nonlatex material (Tactylon, Smart Practice, Phoenix, Arizona).

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Acyclovir to Treat Varicella

THE USE OF ORAL ACYCLOVIR as a routine treatment of primary varicella in otherwise healthy children is controversial. Several reports arising from a large, multicenter trial comparing the use of acyclovir with that of placebo have shown a significant decrease in morbidity in children and adolescents given acyclovir, 20 mg per kg four times per day (to a maximum of 800 mg 4 times a day), when initiated within the first 24 hours of rash. Treated children had about one day less fever, a decreased constitutional illness score by day 4 of the disease, more rapid cutaneous healing, and fewer skin lesions (median of 336 versus 500). No study has shown a decrease in serious complications, but this may be due to the relatively low complication rate compared with the number of patients studied. A study of oral acyclovir as a postexposure prophylactic treatment recently suggested that its use may prevent or ameliorate chickenpox in children with exposure to varicella. This treatment strategy will probably be relevant in only a few cases where the precise time of exposure is known, and the adequacy of long-term immunity in prophylactically treated patients is not known.

The detractors of the routine use of acyclovir have raised several legitimate concerns. First, treatment in children has been shown to be efficacious only when initiated in the first 24 hours of infection. Thus, many patients who are seen later in the course of the disease (when the actual severity of the disease can best be assessed) are not candidates for therapy. Moreover, the effect of the treatment, although statistically significant, is modest at best, an effect that is even more striking when compared with the efficacy of varicella vaccine: vaccinated children who do become infected have a median of 18 skin lesions compared with 336 in those treated with acyclovir. The expense of a course of acyclovir depends on the weight of the child and the pharmacy used, but varies from $25 to $100. Because the expense of lost wages and productivity of parents who must stay home because of their child's illness is enormous, a strategy employing vaccination will probably be more cost-effective than the widespread use of oral acyclovir. Another concern, at present conjectural, is the potential for the emergence of acyclovir-resistant strains, such as those seen in immunodeficient patients. Finally, although the mean varicella antibody titers a year after treatment with acyclovir are no different from those in untreated patients, some authors have speculated that acyclovir-treated patients may ultimately be more susceptible to zoster or reinfection.

The American Academy of Pediatrics Committee on Infectious Diseases, while noting that a decision to treat must be based on a discussion between a physician and family, has recommended against this routine treatment of all children. The committee suggests considering oral therapy for certain groups at increased risk for severe varicella or its complications, if therapy can be initiated within 24 hours after the onset of rash. These include adolescents; children receiving short, intermittent, or aerosolized corticosteroids; children older than 1 year with a "chronic cutaneous or pulmonary disorder"; and those receiving ongoing salicylate therapy. Intravenous acyclovir is recommended in immunocompromised children.

The data regarding treatment in children younger than 12 months are insufficient to make any recommendations. Some have also recommended treating children who have been infected from a household contact because these "secondary" cases are often more severe, but this recom-

mendation is controversial. The prophylactic use of acyclovir in these cases may ultimately prove to be useful.

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Polymerase Chain Reaction in Dermatology

DEVELOPED IN San Diego less than ten years ago, polymerase chain reaction (PCR) has played a major role in addressing an astounding variety of problems, many referable to dermatology.

Polymerase chain reaction can detect even minute amounts of biomedical, archaeologic, and forensic material efficiently, economically, and in only a few hours. It involves three steps endlessly repeated in the same vessel until the desired amount of material has been obtained by exponential amplification.

Deoxyribonucleic acid is first denatured by heat, usually at 94°C for one minute. Resulting oligonucleotide primers ("oligos"), specifically designed for identifying the single-stranded DNA sequences to be isolated and amplified, range in length from 15 to 25 base pairs. The polymerizing step then rapidly amplifies the desired sequence by a chain reaction dependent on a heat-stable polymerase derived from an organism, *Thermus aquaticus*, the so-called Taq polymerase.

By repeated cycling of this reaction, the quantity of the substance of interest is increased exponentially. Even single molecules can be identified and made available in large quantities within a few hours. This has had an enormous effect on the ability to study an already wide range of materials of biomedical interest.

Obviously a technique so exquisitely sensitive as PCR is subject to the risk of false-positive reactions, so testing must be carried out under the most rigorous of laboratory conditions. Contamination by even minute amounts of extraneous substances must be meticulously avoided. The use of new glassware for each run may be necessary. Appropriate positive and negative controls are mandatory. False-negative reactions can also be encountered. For example, in the search for certain organisms or cell products in histologic material, sensitivity may be lost because the material sought may be denatured by the use of inappropriate tissue fixatives.

Methods for quantitative PCR are being perfected, but PCR has already been applied to a wide range of problems of dermatologic interest. With its use, many organisms have been detected in skin specimens and histologic sections. Polymerase chain reactions may play an increasingly important role in the early diagnosis of Lyme disease because serologic tests and traditional bacterial isolation are not reliable in early stages of the disease. Borrelia organisms have been recovered from early skin lesions, from serum, and even from wood ticks. Another important application has been the discovery of the causative organism, *Rochalimaea* species, of bacillary angiomatosis. The same organism has been more recently found in cases of cat-scratch fever, confirming the clinical observation that many patients with the acquired immunodeficiency syndrome in whom a bacillary angiomatosis developed have had exposure to cats. Tubercle bacilli have recently been isolated by PCR from lesions of erythema induratum, long thought to be of tuberculous origin, but never before proved because of the small number of organisms present in biopsy specimens from these lesions. Using PCR, the herpes simplex virus has been recovered from skin lesions of erythema multiforme, making even firmer the relationship between herpes simplex virus and recurrent episodes of that eruption. In another report, herpes simplex virus type 6 was reported recovered from skin lesions of patients with Langerhans cell histiocytosis.

Polymerase chain reaction has proved useful in the rapid typing of the human papillomavirus, helping to clarify its relationship to certain forms of squamous cell carcinoma. Using PCR, the human immunodeficiency virus has been identified in Langerhans cells of the epidermis and in neonates where serologic methods may be unreliable and viral cultures unproductive. It also can detect the human immunodeficiency virus in donor blood. Other applications to the microbiology of skin diseases have been the identification of organisms in biopsy specimens of infections with cytomegalovirus, leishmaniasis, and the human T-cell leukemia virus type I. It should be added that PCR is chiefly a research tool at this time and is not yet widely available.

Polymerase chain reactions are also proving to be of great value in the prenatal diagnosis of a number of genetic disorders of dermatologic interest. To some extent, PCR has obviated the use of more traditional methods of prenatal diagnosis, such as amniocentesis, chorionic villus sampling, or fetal umbilical blood sampling, all of which carry at least a small risk to the fetus or the pregnant woman. Polymerase chain reactions can be used to isolate and analyze even minute amounts of fetal genetic material. A recently presented striking example of this capability was in the PCR-aided isolation of fetal DNA from nucleated cells in the circulating blood of the mother. Genetic disorders with cutaneous features in which point mutations in genes have been identified by the PCR reaction include albinism, neurofibromatosis, xeroderma pigmentosum, chronic granulomatous disease, a number of connective tissue disorders, several of the porphyrias, and hereditary angioedema.

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Interferon

INTERFERONS ARE PROTEINS discovered more than 30 years ago that act as an element in the body's natural defenses. First noted for their antiviral effects, interferons also show antitumor and immunologic properties. Currently, three types of interferons are recognized: α, β, and γ.

Recombinant and natural interferons are available for clinical use. In the United States, interferons have received Food and Drug Administration (FDA) approval for treating hairy cell leukemia; condyloma acuminatum; Kaposi's sarcoma in patients with the acquired immunodeficiency syndrome; and non-A, non-B (type C) hepatitis. Interferons have also shown effectiveness in basal cell carcinoma, squamous cell carcinoma, and melanoma, with approval for intralesional interferon for basal cell carcinoma in more than 20 other countries, including Canada and Australia.

Interferons were initially noted in dermatology for their role in the treatment of condyloma acuminatum. Despite numerous nonsurgical and surgical treatments, genital warts continue to have a high rate of recurrence after treatment at follow-up several months later. Both recombinant interferon alfa-2b (Intron A, Schering Corporation) and human leukocyte-derived interferon alfa-n3 (Alferon N Injection, Interferon Sciences) have been effective for intralesional treatment of genital condyloma acuminatum. Combination therapy using laser surgery, electrosurgery, or cryosurgery followed by the intralesional administration of interferon appears to enhance results.

Primary superficial and nodular basal cell carcinomas have been successfully and safely treated with intralesional interferon alfa, with an overall cure rate of at least 80% based on excision of the treated site a year after therapy. The current treatment regimen recognized is 1.5 million IU administered intralesionally three times a week for three weeks (9 total injections; total dosage of 13.5 million IU). Patients need to have the appropriate long-term follow-up, just as with any therapy for their basal cell carcinoma. With the current lack of FDA approval, however, it is recommended that a small punch biopsy be taken at about three months after treatment to provide histologic evaluation in addition to clinical follow-up.

Squamous cell carcinomas also appear to respond to the intralesional administration of interferon alfa-2a. In a recent trial, cure rates were better than those achieved with basal cell carcinoma, with further studies pending to demonstrate repeatable results. Combination therapy for squamous cell carcinoma with interferon alfa-2a (Roferon-A, Hoffmann-LaRoche) and tretinoin may offer an increased response for patients with advanced squamous cell carcinoma of the skin.

Response rates for the treatment of metastatic melanoma with interferon (primarily interferon alfa) were initially similar to those of other therapies, with a range of 16% to 22%. Recently the use of interferon alfa plus a four-drug regimen (dacarbazine, vincristine sulfate, bleomycin sulfate, and lomustine) demonstrated a higher response rate and may offer promise with patients with metastatic melanoma.

Side effects related to intralesional interferon use may be systemic or local. For the most part, these are mild to moderate at the routine doses, and most commonly consist of fever, malaise, headache, and arthralgia. The use of acetaminophen can ameliorate a number of the systemic reactions, and discomfort can be decreased by giving treatment late in the day.

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Silicone Use in Keloids

KELOID AND HYPERTROPHIC SCARS are both abnormal tissue responses to injury, sometimes as mild as acne papules. They are racially related, with an incidence as high as 15% in black African Americans. Keloids can be distinguished from hypertrophic scars in several ways. They are slower to develop, sometimes showing up months after the damage; they overgrow the margins of the original wound; they do not spontaneously regress; and they frequently cause symptoms such as pain, itching, and burning. The precise pathogenesis remains uncertain, but may be related to abnormal levels of tissue growth factors from new blood vessels.

These scars have been notoriously difficult to treat. Many painful and expensive therapies have been tried with varying success. Cold-steel excision with or without closure has recurrence rates of about 80%, and the once highly touted carbon dioxide laser has not been much better. The intralesional administration of corticosteroids every three weeks for periods of as long as six months has improved the results somewhat.

A novel approach using silicone products has been developed recently. The original papers reported the use of silicone creams in burn scars and contractures. Since then there have been several reports of silicone gel sheets and silastic gel sheets used preventively in high-risk patients, in both new and old keloids, and even after the excision of a keloid scar during the healing phase. A recent Israeli study showed 72% moderate to excellent results, with only a 12% no-response rate. Other reports have shown adjunct benefit with pressure garments and intralesional corticosteroids. There are reports of decreased symptoms within two hours of wearing the sheeting and more permanent benefits after several months.

Similar results have been reported with the use of silicone creams, silicone gel sheeting, and the rubbery silastic gel sheeting, even though this less flexible form does not have close contact with the surface irregularities of the scar. The silastic gel sheeting has the advantage of being relatively indestructible, so one sheet will frequently last through the entire course of therapy. The other products rarely last a week before they require replacement.

The mechanism of action remains uncertain. Static electricity of hundreds of volts per inch has been demonstrated with both the silicone and silastic gel sheeting. With reports showing increased mast cells within keloids—and suggesting this as the cause of symptoms—and other reports showing both an effect of mast cells on collagen production and a decrease in mast cell numbers by electrical stimulation, this has been proposed as the mechanism of action. Other investigators have cited differences in permeability to water and hydration as the mechanism of action.

Biopsy specimens taken before and after successful therapy show little structural change of scar tissue. Of even more interest, there is no evidence of silicone in body tissue with any of the forms including the silicone creams. With the current concern over silicone implants, this can be of great importance. There is no need for pressure increase, and irritation can be easily controlled without sacrificing efficacy.

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Management of Capillary Hemangiomas

CAPILLARY OR STRAWBERRY HEMANGIOMAS are the most common benign vascular tumor of neonates. The incidence is estimated to be 1.0% to 2.6% of births and as high as 10% in the first year of life. If present at birth, the lesion appears as a faint red to violaceous macule surrounded by a white halo. A capillary hemangioma proceeds through distinctive phases: a proliferative phase during the first year, a stable period, and in the course of months to years, involution even in the absence of therapy. A useful rule of thumb is that 50% of lesions regress completely within five years, 70% within seven years, and the remainder continue to fade until age 10 to 12.

The management of capillary hemangiomas remains conservative because most of these lesions involute spontaneously. Frequently observing patients in the proliferative growth phase, measuring the size of the lesion, and obtaining serial photographs have become the standard of routine care. Parents require repeated reassurance as to the benign nature and evolution of these tumors.

Active therapy is reserved for the more aggressive lesions; the method of treatment must be chosen on an individual basis. A regimen of oral steroids at an initial dosage of 2 to 4 mg per kg per day is indicated in rapidly enlarging lesions that may seriously distort facial features, interfere with normal physiologic functions (vision, respiration, eating, or hearing), and are associated with ulceration and recurrent bleeding. High-dose oral prednisone therapy should be continued for four weeks, followed by alternate-day therapy using the same or doubled dosage for another four to six weeks, with subsequent gradual tapering of the dosage as needed. Involution begins in the second or third week of treatment and continues into the second month. If rebound growth of the hemangioma occurs, a second or third course of oral corticosteroids may be necessary. Immature, proliferating hemangiomas are far more responsive to steroid treatment than stable or involuting lesions. Softening, lightening of color, and a diminished rate of growth are the indicators of responsiveness to treatment. Upper eyelid hemangiomas present a special problem because they may cause substantial visual disturbances such as strabismus, amblyopia, astigmatism, and anisometropia. If the visual axis is occluded, or vision is affected, intralesional corticosteroids, such as triamcinolone acetate and betamethasone sodium phosphate or acetate, are administered to the eyelid hemangiomas by ophthalmologists. Excellent response to such treatment has been reported in one series. Recently reported side effects of this intralesional treatment include pigmentary and atrophic changes of the epidermis, eyelid necrosis, retinal artery occlusion, adrenal suppression, and growth retardation. Other severe vision-threatening or life-threatening hemangiomas unresponsive to corticosteroids may also be treated subcutaneously with interferon alfa-2a in a dosage ranging from 1 million to 3 million units per m^2.

Lasers have a definite role in the treatment of capillary hemangiomas. The vascular-specific (585 nm), pulsed (450 microseconds), tunable dye laser has been effective in preventing enlargement and promoting involution when treatment is initiated early and the hemangioma is elevated 3 mm or less. This laser also promotes wound healing in ulcerated hemangiomas of the anogenital and intertriginous areas. Ulcerations of less than 20 mm heal within two weeks after a single treatment, and the pain associated with the ulceration diminishes within 24 hours. Vascular-specific pulsed-dye lasers function by selective photothermolysis of capillary-sized blood vessels. They are safe, effective, and their use is associated with a minimal risk of scarring.

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Ozone Depletion—Is the Sky Falling?

OZONE IS A NATURALLY OCCURRING molecule found in the stratosphere (15 to 50 km above the earth's surface). Ozone and oxygen absorb most of the ultraviolet radiation transmitted to the earth. Substantial ozone depletion could result in increased UV irradiation at the earth's surface, with many possible deleterious effects, including an increased incidence of skin cancers and cataracts.

Halocarbons have been impugned as the main cause of ozone depletion. These include both chlorofluorocarbons (CFCs) and halons. Both are short carbon chains, CFCs being saturated with predominantly chlorine and halons with bromine. Chlorofluorocarbons largely result from manufacturing processes, including those involving air-conditioning coolants, foam extrusion, and industrial solvents. Halons come from both natural sources, such as seawater, and industrial processes involving fire extinguishers.

When halocarbons reach the stratosphere, they act as a catalyst for the destruction of ozone. The chlorine and bromine are not consumed. Each chlorine molecule has a half-life of 75 years and may destroy about 100,000 molecules of ozone.

Although somewhat controversial, there is a fair consensus that the ozone layer is thinning. Satellite measurements report worldwide ozone depletion of at least 3% since 1978, with some estimates substantially higher. This depletion is unevenly distributed, being as much as 50% at the poles and about 7% in the temperate areas. No ozone depletion has been reported in the equatorial regions. There is an important seasonal variation, with ozone levels being lowest in the winter and highest during the summer.

Increased amounts of UV radiation, especially UVB, will reach the earth's surface as a result of ozone depletion. It is estimated that for every 1% decrease in ozone, there will be a 2% to 6% increase in the incidence of both basal cell and squamous cell carcinoma. More important, it is estimated that there will be about a 1% increase in the incidence of melanoma for each 1% depletion in ozone. As ultraviolet light is also implicated in causing cataracts, as many as 2.8 million additional cataracts could occur worldwide by 2075.

Despite the documented decreased ozone levels, no increases in ground-level UVB had been recorded in temperate regions until a recent report. For the first time, UVB levels in a temperate region have been shown to be increasing by 5% per year since 1988. There have also been recent intermittent reports of increased UVB at ground levels in the Antarctic. The cold temperature at the poles may predispose to the ozone depletion and the resultant increased UVB.

There are some reassuring factors. Smog, pollution, and particulate material in the atmosphere all help to absorb or disperse UVB. Indeed, some models even predict decreased UVB levels at ground level despite ozone depletion. Further, even if the amount of UVB doubled or tripled in northern and southern latitudes, these areas would receive less UVB than the equatorial regions currently receive. Seasonal ozone variation is also partially protective. Ozone is created by photochemical interactions, so as UV irradiation increases—that is, summertime—increasing amounts of ozone are produced.

Approaches to dealing with ozone depletion include phasing out all ozone-damaging halocarbons by the year 2000, following an international agreement signed in 1988 by 42 countries. This should decrease the amount of artificial halocarbons in the atmosphere, although the effect of natural halocarbons such as from the eruption of Mount Pinatubo in the Philippines is unknown. Chlorofluorocarbon substitutes are being actively developed, although at the present time they appear to be more expensive and less efficient in industrial processes. The recycling of CFCs in compounds such as home and auto coolants is becoming mandatory in most states. Many new cars are using an air-conditioning system free of CFCs. Finally, risks posed by increased UVB at the earth's surface can be partially offset by protective measures such as sunscreens, eyewear, and appropriate clothing.

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Recent Developments in the Treatment of Human Papillomavirus

WARTS HAVE BEEN RECOGNIZED since Greek and Roman times. Despite recent advances in recombinant DNA technology, which have allowed the identification of more than 60 different genotypes of human papillomavirus (HPV), current treatment remains controversial and often disappointing.

With recent polymerase chain technology, HPV DNA can be identified in tissues without clinically apparent lesions (so-called subclinical lesions). Dormant HPV has been identified in tissues using this technology (latent lesions). Our failure to cure HPV infections, many think, results from our inability to resolve these lesions. Unfortunately, few studies demonstrate consistent resolution of subclinical and latent lesions by any treatment method.

Recently the malignant transformation potential of HPV has come to the forefront and several questions have been raised, not only about the malignant potential of clinical HPV lesions, but also about subclinical and latent lesions. Papillomavirus types 6, 11, 16, and 18 have been implicated as a possible cause of condylomata acuminata (genital warts). More important, HPV types 6 and 11 have been associated with low-grade dysplasia of the cervix, whereas types 16 and 18 are associated with high-grade dysplasia, carcinoma in situ, and invasive carcinomas of the cervix. Human papillomavirus types 6, 11, 16, and 30 have been detected in laryngeal squamous cell carcinomas. Some lesions of epidermodysplasia verruciformis (a rare, chronic skin disorder associated with HPV types 5, 8, 14, 17, and 20) are thought to undergo transformation to squamous cell carcinoma.

Concerns about HPV tumorigenicity and unacceptable recurrence rates with standard treatment methods (cryosurgery, carbon dioxide laser, electrosurgery, surgery, salicylic acid, trichloroacetic acid, podophyllin, fluorouracil [5-fluorouracil], and bleomycin sulfate) led to the search for other therapeutic options.

Interferons are cytokines—immunoregulatory proteins

secreted by cells—possessing antiviral activity. Initial reports in 1974 described promising results in the management of HPV plantar warts with the use of interferon alfa ointment. A multicenter trial using parenterally administered interferon showed that only 19 of 77 patients with genital warts had the complete clearance of lesions. Other centers have reported better success rates (as high as 53%) with parenteral interferon, but at doses where patients had more side effects. This apparently narrow therapeutic window led to the use of intralesional interferon alfa. A multicenter, double-blind, placebo-controlled trial using intralesional interferon alfa showed that 62% of treated patients were completely free of lesions, in contrast to 21% in the control group. More important, 75% of complete responders remained free of lesions 18 months after therapy, and side effects were substantially reduced. An interesting note is that one study found that 50% of patients given interferon had concomitant improvement in untreated lesions. This study suggests that intralesional interferon may reduce subclinical and latent lesions that are instrumental in the recurrence, as well as persistence, of HPV. One study suggests that intralesional interferon has an effect on HPV-associated cervical intraepithelial neoplasia and, in some cases, can achieve complete resolution of lesions. We are several studies away from proving a clear advantage of this drug in the treatment of HPV, but data so far indicate that it may provide an alternative to the disappointing recurrence rates and malignant transformation currently experienced.

Another possible therapy is the systemic use of retinoic acid, which may have potential for reducing recurrence and malignant transformations by preventing infectivity by HPV. One study has shown that physiologic concentrations of retinoic acid suppressed the infectivity of HPV in human keratinocytes, as well as the proliferation of previously infected human keratinocytes. The use of etretinate resolved extensive warts in immunosuppressed patients.

Although several therapeutic options are available in the treatment of HPV, no one method offers a clear advantage. Commonly used treatments, although offering convenience and cost savings, do not, in general, reduce recurrence rates, and they fail to address the issue of malignant transformation. The therapies described in this epitome could provide more acceptable recurrence rates and lower tumorigenicity, but there simply are not enough supportive data at this time. Furthermore, the relationship between HPV and cancer is an evolving area and, as it becomes more clearly defined, so should our treatment strategies.

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α-Hydroxy Acids for Skin Rejuvenation

α-Hydroxy acids are organic acids naturally found in fruits (malic, citric, and tartaric acids), sugar cane (glycolic acid), and sour milk (lactic acid).

In the 1970s, these acids were reported to decrease corneocyte adhesion, allowing removal of the thick scale of ichthyosis, psoriasis, and seborrheic keratoses. In higher concentrations, epidermolysis (splitting of the epidermis from the dermis, or "peeling") occurs. Because they lack systemic toxicity, concentrated α-hydroxy acids began to be used by dermatologists in place of other peeling agents such as phenol, trichloroacetic acid (TCA), and resorcinol to treat photoaging, especially to reduce hyperpigmentation and fine wrinkles, to remove early actinic and seborrheic keratoses, and to give the skin improved texture and a youthful glow—in other words, as agents for freshening peels.

The proposed mechanisms of these improvements include thinning of the stratum corneum, dilatation of superficial blood vessels, and thickening of the actinically thinned epidermis and upper (papillary) dermis. Recent work suggests that α-hydroxy peels stimulate mast cell degranulation. It is hypothesized that the liberated mast cell products can stimulate dermal fibroblasts to produce increased amounts of collagen and elastin, regenerating youthful-appearing skin.

One method of treatment is to apply an α-hydroxy acid in a 20% to 70% concentration to skin that has been pretreated with a 5% to 10% solution of α-hydroxy acid or tretinoin (Retin-A) for two to four weeks and then scrubbed with acetone, alcohol, soap and water, or an α-hydroxy acid cleanser. The depth of peel depends on the time of exposure, whether the acid is buffered or unbuffered, the vigor of preparation, sebaceous gland activity of the patient, and personal idiosyncrasy. This is considered a superficial or very superficial peel. Repeated peels at weekly or monthly intervals may give improvement comparable to mid-depth TCA peels with less pain and crusting than the single, more intense peel.

Most clinicians feel that postinflammatory hypopigmentation and hyperpigmentation are less than with phenol or TCA, but there is greater patient-to-patient variability with α-hydroxy acids, so peels must be done cautiously at first. Dark-skinned patients are at a higher risk for pigmentary problems. Because the depth of penetration is time-related, overexposure to α-hydroxy acids used in peels can result in severe burning with subsequent scarring.

It has yet to be determined if the reversal of photoaging by α-hydroxy acid peels is nonspecific or can be duplicated by any method that causes chronic low-grade inflammation such as dilute TCA, tretinoin, salicylic acid, resorcinol, carbon dioxide slush, and epidermabrasion with rough-surfaced pads, sponges, pumice stones, or scrubbing granules.

In addition to the use of α-hydroxy acids in high concentration for in-office peeling, lotions and creams

containing lactic and glycolic acids in particular have been claimed to reverse some of the changes of photoaging when used for 2 to 12 months. Studies are in progress to determine if these products survive double-blind evaluation.

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Alerts, Notices, and Case Reports

Seronegative Hepatitis C Virus Liver Failure Following Transplantation of a Cadaveric Heart

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WE REPORT THE FOLLOW-UP and outcome of a previously reported case of a patient who contracted hepatitis C virus (HCV) infection from a transplanted heart. The patient's hepatitis progressed to cirrhosis and liver failure in less than two years. Detectable antibodies to HCV never developed, but HCV RNA detection by reverse transcriptase polymerase chain reaction (PCR) revealed 10^8 viral particles per milliliter of serum. Post-transplantation immunosuppressive therapy may cause standard HCV immunoassays to be falsely negative. This case suggests that severe HCV hepatitis with liver failure may result from organ transplantation.

Report of a Case

In 1991 Schuch and co-workers reported a case of post-transplantation hepatitis in a patient receiving a heart from a donor who was seropositive for antibody to HCV (anti-HCV).[1] The patient was a 46-year-old man with a history of two myocardial infarctions. Before transplantation he had coronary artery bypass grafting in February 1989, and later that same year he suffered his third acute myocardial infarction, leaving him with an ejection fraction of about 0.15 (15%). Coronary angiography showed occlusion of all grafts. He was placed on the list for a heart transplant, and in April 1990 he underwent orthotopic heart transplantation. Before transplantation, the patient was found to have antibodies to cytomegalovirus (CMV) but not to hepatitis B surface antigen (HBsAg), and he had normal aminotransferase levels. The heart donor tested negative for antibodies to CMV, HBsAg, the human immunodeficiency virus, and the human T-lymphotropic virus. Two units of packed erythrocytes, two units of fresh-frozen plasma, and one unit of single-donor plateletpheresis were given during the transplantation. The patient was discharged two weeks after the operation in good condition. At that time, immunoassays for HCV antibodies were not widely available, but later the heart donor's stored serum specimen was found to be reactive for anti-HCV on first- and second-generation enzyme-linked immunoassays (EIAs) and first- and second-generation recombinant immunoblot assays (RIBAs). All donors of blood products given during transplantation were nonreactive for anti-HCV using the same assays.

Mildly elevated levels of alanine aminotransferase (ALT, 56 U per liter; normal, 0 to 45), and aspartate aminotransferase (AST, 89 U per liter; normal, 0 to 40) were noted in early June 1990. These values gradually increased over the next several weeks. He was readmitted in mid-August 1990 with jaundice, anorexia, and nausea. His AST level was 208 U per liter, the ALT level was 178 U per liter, γ-glutamyl transferase was 166 U per liter (normal, 7 to 33), alkaline phosphatase was 449 U per liter (normal, 42 to 139), and bilirubin was 160 μmol per liter (9.4 mg per dl [normal, 3 to 20]). A liver biopsy showed acute cholestatic hepatitis consistent with viral infection (Figure 1). No evidence of CMV infection was seen. The patient did not have antibodies to HBsAg, hepatitis B core antigen, or hepatitis A virus immunoglobulin M. He subsequently tested negative for anti-HCV by first- and second-generation EIAs and first- and second-generation RIBAs. He was discharged and managed conservatively. At the time of the initial report, his amino-

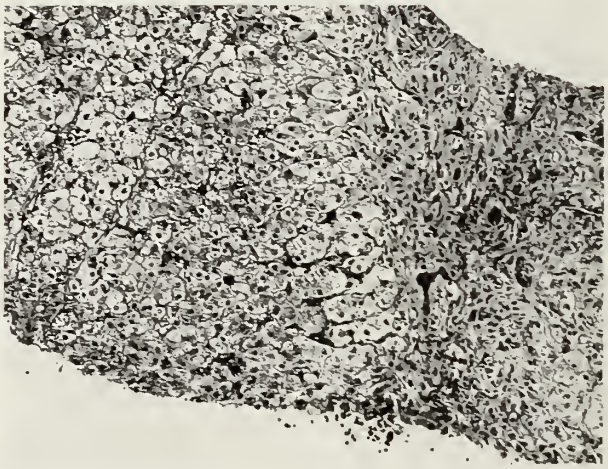

Figure 1.—An initial liver biopsy taken 3 months after aminotransferase levels became elevated shows hepatocyte ballooning and portal inflammation (hematoxylin and eosin stain, original magnification × 130).

(Hayashi PH, Fernando L, Schuch DR, et al: Seronegative hepatitis C virus liver failure following transplantation of a cadaveric heart. West J Med 1994; 160:368-371)

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
anti-HCV = antibody to hepatitis C virus
AST = aspartate aminotransferase
CMV = cytomegalovirus
EIA = enzyme immunoassay
HBsAg = hepatitis B surface antigen
HCV = hepatitis C virus
PCR = polymerase chain reaction
RIBA = recombinant immunoblot assay

transferase levels were still three to six times the upper limits of normal, but he was doing relatively well as an outpatient. He was presumed to have HCV hepatitis, but no definitive diagnosis could be made because he remained seronegative for anti-HCV.

In July 1991, severe steatorrhea developed; the patient's fecal fat measured 254 mmol per day (72.3 grams per 24 hours) on a 100-gram fat diet. Despite an extensive workup that included small bowel biopsies, stool analysis and cultures, D-xylose absorption analysis, and numerous radiographic examinations, no cause could be found. He was treated with various high-dose pancreatic enzyme supplements, antibiotics for possible bacterial outgrowth, and antidiarrhea medications without lessening of the steatorrhea.

Because of a persistent lack of reaction to anti-HCV by EIA and RIBA, reverse transcriptase PCR for HCV RNA was done and detected 10^8 viral particles per milliliter of the patient's serum. A second liver biopsy in August 1991 showed portal inflammation and early cirrhosis (Figure 2). A trial of interferon alfa, 3 million units subcutaneously three times per week, was given without a notable decline in aminotransferase levels.

The patient's condition gradually deteriorated, with frequent hospital admissions for dehydration due to persistent diarrhea. Liver function continued to worsen, with his bilirubin level increasing to 205 μmol per liter (12 mg per dl) and the albumin value falling to 19 grams per liter (1.9 grams per dl). Throughout his course he remained on a regimen of prednisone and cyclosporine, but the azathioprine was discontinued. During his last hospital stay in March 1992, he was noted to have hepatic encephalopathy and ascites. He was discharged, and after discussion with the family, a less aggressive approach to his illnesses was adopted. The patient died at home on March 27, 1992.

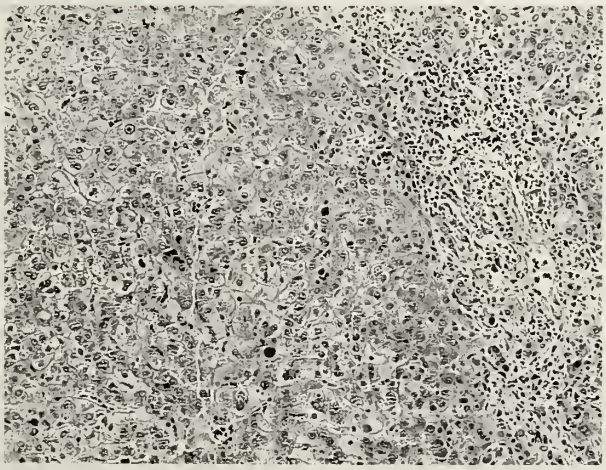

Figure 2.—A second liver biopsy taken 15 months after the aminotransferase levels became elevated shows portal-to-portal fibrosis and periportal lymphocytic infiltration (hematoxylin and eosin stain, original magnification × 130).

An autopsy revealed submassive necrosis of the liver with micronodular cirrhosis and cholestasis (Figure 3). Immunohistochemical stains for CMV were negative. The small and large intestines were normal both grossly and microscopically. The pancreas showed peripheral fat necrosis but a normal complement of islet cells and minimal periductal fibrosis. At the time of his death, the patient remained anti-HCV seronegative by second-generation EIA and RIBA.

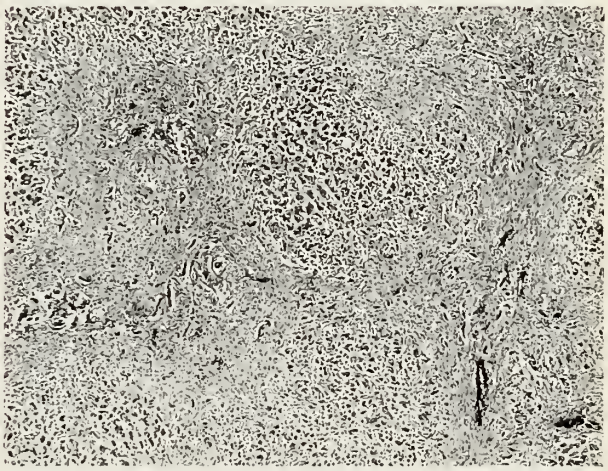

Figure 3.—A postmortem liver specimen shows micronodular cirrhosis (hematoxylin and eosin stain, original magnification × 58).

Discussion

This patient appears to have contracted HCV from the cadaveric heart, based on both serologic tests and reverse transcriptase PCR. All blood products given to the patient before and during transplantation have since been nonreactive to anti-HCV by EIA and RIBA. The heart donor's serum was reactive to anti-HCV by EIA and RIBA, and our patient's pretransplantation serum specimen tested negative for HCV antibodies. At the time of the initial report, HCV PCR data were not available. The patient's subsequent rapid demise to liver failure is noteworthy.

The rate and severity of HCV transmission by organ transplantation remain controversial. Several studies involving patients with kidney transplants found a high prevalence of anti-HCV after transplantation,[2-4] but in few of these studies were assays for HCV RNA done. None demonstrated substantial organ transmission. Attempts were made to show liver transplant transmission using both serologic evidence and reverse transcriptase PCR.[5] Post-transplantation hepatitis occurred more frequently than expected if the organ donor was HCV-positive by

EIA. The seroconversion rate in those with post-transplantation hepatitis was 25%. The lack of definitive evidence for organ transmission of HCV has sparked much debate about the safety of transplanting organs from HCV-seropositive donors.[6-9] Investigators studied 58 recipients of organs from 31 RIBA-reactive donors and concluded that "HCV transmission by organ transplantation is low" and clinically unimportant.[10] Unlike our patient, some of the patients in these studies were probably infected before transplantation. Also, blood product donors often were not tested for HCV antibodies. Therefore, the transplanted organ cannot always be implicated as the sole means of HCV transmission.

A possible explanation for conflicting data on whether anti-HCV-reactive organ donors can transmit infection is that donors with no epidemiologic evidence for contracting HCV nor any other surrogate markers for non-A, non-B infection have a false-positivity rate on EIA of about 60%. If the EIA signal to cutoff ratio is greater than 5, the false-positivity rate drops to less than 7% based on RIBA and PCR confirmatory testing. If the signal to cutoff ratio is less than 5, the false-positivity rate is 91%.[11] A similar correlation between the EIA signal:cutoff ratio and the RIBA confirmatory test is seen in organ donors.[10] In our patient, the heart donor's serum signal:cutoff ratio was greater than 5.

After transplantation, our patient never had detectable antibody to HCV, but reverse transcriptase PCR done on serially diluted serum showed a minimum of 10^8 viruses per milliliter. The PCR assay employed is capable of detecting 1 to 5 HCV RNA molecules per milliliter.[11] Therefore, substantial viremia developed in our patient after the transplantation. The lack of seroconversion to HCV is likely due to his immunosuppressive medications. Several studies have indicated that HCV tests are unreliable in patients with liver transplants, leaving HCV RNA detection by reverse transcriptase PCR as the most reliable screening tool to detect infection.[12-14]

Little is known about the natural course of post-transplantation HCV hepatitis. Patients with HCV hepatitis have had a 44% rate of allograft damage a year after liver transplantation.[13] Histologic features ranged from chronic persistent hepatitis or lobular hepatitis to chronic active hepatitis. No cirrhosis was mentioned. In another study, 13.8% of patients with liver transplants who were observed for one to five years had histologically proved hepatitis thought due to non-A, non-B hepatitis, but none progressed to cirrhosis.[15] In one of the studies mentioned earlier, 13 of 46 recipients of kidneys from donors who were anti-HCV-reactive by RIBA had either acute or chronic post-transplantation hepatitis, but none had notable morbidity from liver dysfunction.[10] In contrast, in another study 12% of patients with HCV hepatitis after transplantation had cirrhosis,[12] but their clinical course was not discussed.

Severe post-transplantation HCV hepatitis with liver failure is rare. There have been reports of recurrent fulminant liver failure in patients who received an organ transplant for fulminant non-A, non-B hepatitis.[16,17] In each of these patients, however, a source for graft failure other than HCV reinfection was present—for instance, thrombotic graft infarction or coliform infiltration of the graft. Some think that there is an increased incidence of graft coagulative necrosis after transplantation for non-A, non-B fulminant hepatic failure, but that the precise role of HCV infection cannot be established.[18] In a recent editorial, it was noted that no cases of recurrent fulminant disease were reported in a similar group of 23 patients.[19] The conclusion was that "the host immune response, so central to the pathogenesis of the initial illness, is attenuated in the liver transplant recipient and thus a fulminant course is rare."[19(p642)] In another report, six patients were infected with HCV before liver transplantation. Five had antibodies to HCV after transplantation, with one patient having self-limited viral hepatitis and another having severe liver dysfunction with cirrhosis in two subsequent allografts.[20]

In our patient, transplantation from the HCV-seropositive heart donor clearly had a poor outcome, with progression to liver failure and death within 1½ years after aminotransferase levels became elevated. The lack of other causes for liver failure, serologic testing of the donor, and reverse transcriptase PCR results clearly implicate HCV as the source for hepatitis and cirrhosis despite immunosuppressive therapy. One may argue that our patient had a more aggressive course because he did not receive a liver transplant. With his own liver, his major histocompatibility complex-restricted T lymphocytes could more readily recognize HCV-infected hepatocytes and cause severe cytotoxicity. Recent data do not support such reasoning. As mentioned earlier, no serious liver dysfunction was found in patients with hepatitis after kidney transplantation when the donor was anti-HCV-reactive by recombinant immunoblot assay. Seven of seven heart transplant recipients also had normal ALT levels, as opposed to three of three liver transplant recipients who had elevated ALT levels when the donors were anti-HCV-reactive.[10]

In this case of severe, seronegative HCV hepatitis and liver failure in a heart transplant recipient, the patient was most likely infected with HCV by the transplanted heart. Post-transplantation immunosuppression likely caused him to be seronegative and probably contributed to his severe liver disease and high viral titer. We concur with other investigators that HCV reverse transcriptase PCR remains the best tool to detect and study HCV in patients with immunosuppression.

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Successful Medical and Psychological Management of Recurring Chest Pain and Frequent Hospital Admissions in a Patient With Coronary Artery Disease

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PATIENTS WITH coronary artery disease who have symptoms or disability out of proportion to the objective findings present a frustrating dilemma. They do not respond to usual cardiac treatments, visit their physicians frequently, are frequently admitted to hospital to rule out myocardial infarction (MI), and have repeated diagnostic testing to quantify ischemia and to redefine coronary anatomy. Because of their known coronary artery disease and possibly life-threatening symptoms, they tend to receive episodic acute care in emergency departments, intensive care units, and cardiac testing laboratories.

Psychiatric disorders can influence symptoms, disability, and health care use in patients with chest pain with and without coronary artery disease. For example, 30% to 40% of patients with chest pain with normal coronary angiograms have psychiatric disorders (especially panic disorder, major depression, and somatization disorder) producing symptoms (chest pain, shortness of breath, palpitations) and high health care use, despite a good cardiac prognosis.[1-10] In patients with coronary disease, the prevalence of panic disorder and major depression equals or exceeds that in patients with all other disorders seen in general medical clinics.[11-17] Panic disorder can mimic or aggravate coronary artery disease,[18] and patients with this disease who also have major depression have an increased number of cardiac events, degree of disability, and number of hospital days.[19,20]

Behavioral treatment of chest pain can decrease symptoms, disability, and health care use in patients with[21,22] and without[23-25] coronary artery disease. Treatments are carried out in special inpatient or outpatient settings, with groups or individual patients, usually by interdisciplinary teams of behavioral and medical specialists.

We describe a primary care approach to a patient with severe coronary artery disease in whom the integration of medical and behavioral management resulted in a pronounced reduction of disproportionate symptoms, disability, and health care use.

Report of a Case

The patient, a 43-year-old man, had a large anterior myocardial infarction in October 1985 complicated by ventricular tachycardia, ventricular aneurysm, mural thrombus, and left parieto-occipital embolic stroke. Coronary angiography demonstrated three-vessel disease, and bypass grafting and aneurysmectomy were performed. In June 1986 he had a right ventricular MI with ventricular fibrillation; a second angiogram showed increased narrowing of the right coronary artery. In December 1987 he had a small anterior MI; an angiogram showed a newly occluded small vessel.

The patient's risk factors for coronary disease included tobacco use, hypercholesterolemia, and a family history of early coronary disease. His medications included diltiazem hydrochloride, nifedipine, transdermal nitroglycerin, colestipol hydrochloride, lovastatin, cimetidine, and one aspirin tablet daily.

His parents were alcoholic and divorced when he was 10 years old. He lived with his father who had an MI at age 40 and died of a complication of a coronary bypass operation. The patient did not finish high school. He served in the military from 1966 to 1984 and was stationed in Vietnam but did not see combat. He first had chest pains in 1983, and an exercise electrocardiogram (ECG) was normal. After his first MI he was given a $1,700-per-month disability pension for service-con-

(Gordon GH, Baker LH, Boverman J: Successful medical and psychological management of recurring chest pain and frequent hospital admissions in a patient with coronary artery disease. West J Med 1994; 160:371-375)

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ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
MI = myocardial infarction

nected heart disease. His (fourth) wife of seven years worked as a collections agent for a jewelry store. Both had teenaged children from previous marriages.

On physical examination his blood pressure was 126/66 mm of mercury, his heart rate was 77 beats per minute, his respirations were 14 per minute, and he was afebrile. Pertinent physical findings included a thoracotomy scar, no chest wall tenderness to palpation, and clear lungs to auscultation. His cardiac examination revealed a regular rate and rhythm with an apical S_4 gallop and a 1 to 2/6 systolic ejection murmur at the left sternal border; there was no jugular venous distention or S_3 gallop. The extremities showed no edema. A neurologic examination with formal neuropsychological testing revealed no residual effects of his stroke.

His ECG showed normal sinus rhythm with left axis deviation, normal intervals, and a chronic loss of R waves, ST segment elevation, and T wave inversion anteriorly. A chest x-ray film showed intact sternal wires and was otherwise normal. Low- and high-density-lipoprotein cholesterol levels, complete blood count, sedimentation rate, electrolyte values, liver and kidney function, and the results of thyroid function tests were within normal limits. Tests for hypercoagulability including antithrombin III, anticardiolipin antibody, protein S, and protein C levels were also within normal limits. A ventilation-perfusion scan of the lungs, a Bernstein test, and an upper gastrointestinal series were normal. Voluntary hyperventilation failed to reproduce his chest pain.

During 1988 the patient was admitted to the hospital a total of 27 times (86 days) for chest pain. He typically presented in great distress, clenching his muscles and grimacing, and unable to speak or move. At these times his wife refused to leave the bedside and demanded that he be admitted immediately to intensive care. Typically he was treated with intravenous narcotics, nitrates, and benzodiazepines until an MI was ruled out, and then he was discharged several days later pain free. Angiography in 1988 for recurrent episodes of chest pain showed progressive disease but patent grafts and a mildly decreased left ventricular ejection fraction of 0.44 (44%). Subsequent exercise testing with myocardial thallium imaging consistently showed extensive previous infarctions, minimal ischemic changes, and minimal exercise-induced left ventricular dysfunction.

Psychiatric consultation was attempted during some of his hospital admissions, but was deferred by the treating physicians or declined by the patient. On a later evaluation he did not meet diagnostic criteria for panic disorder, major depression, a somatoform disorder, or other psychiatric disorders.[26] Our strongest diagnostic formulation was that his (realistic) fear of another serious coronary event led to his overinterpreting all symptoms as possibly catastrophic. These fears were reinforced by the health care system, which (appropriately) responded by providing emergent but episodic testing and treatment. Also, he became passive and histrionic about his symptoms because of marital and family stress, and this was frustrating to his physicians. What was missing was an approach that combined medical management of his coronary artery disease with psychological management of his symptoms and behavior in a primary care setting.

Treatment Approach

General

The patient was referred to two of us (G.H.G., a general internist, and L.H.B., a clinical psychologist) for help in developing alternative approaches to his care. The patient and his wife met with us in the general medicine clinic. We acknowledged the presence and seriousness of his symptoms, expressed empathy for his frustration over current treatment efforts, and collaborated with the patient, his wife, and his cardiologists to define thresholds for admission to the hospital and for the administration of medications, including narcotics. By scheduling regular monthly visits, consolidating the number of professionals and decisions involved in his care, and actively involving the patient and his wife in treatment planning, we made his medical care more predictable, less frightening, and less contingent on his having symptoms.

To justify exploring psychosocial aspects of his illness, we noted that many patients with heart disease report that getting upset worsens their chest pains, and we invited him to think about ways that stress might aggravate his heart disease. The patient and his wife were able to identify a number of important stressors. Their children were involved in drug use, truancy, and unwanted pregnancy, and coping with these issues uncovered areas of marital conflict. We suggested that, while we would continue his routine cardiac treatment and be vigilant in evaluating for new heart damage, we could also treat his symptoms by teaching him ways to manage his stress.

Behavioral Treatment

Elements of behavioral treatment in this patient's regimen included the use of a symptom diary,[27,28] relaxation and imagery,[29,30] exposure procedures,[31,32] the setting of realistic goals, and problem-solving techniques.[33]

The patient recorded his chest pain and any concurrent stressors in a diary. By discussing his findings on medical visits, we hoped that he would learn to anticipate worsening of symptoms and intervene through relaxation techniques. The patient readily adapted previously learned relaxation techniques and attempted to apply these during episodes of chest pain, with little initial success.

At the sixth visit the patient collapsed with intense chest pain and was taken to the emergency department. His vital signs were stable, and his ECG showed no new ischemic changes. We observed that the patient kept his eyes tightly closed and was tensing his face, arms, and chest muscles. When asked about this, he replied that he was trying to make the pain go away by concentrating hard on relaxing imagery.

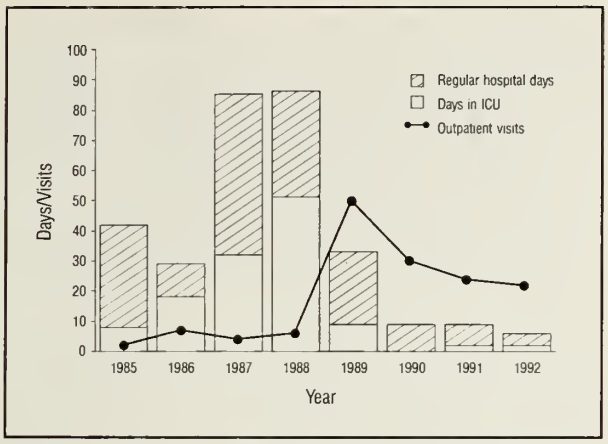

Figure 1.—Annual hospital and clinic use by a patient with recurring chest pain is shown. The patient's inpatient and intensive care unit (ICU) use decreased markedly after primary care-based behavioral treatment was instituted in November 1988. Most clinic visits after that were to the authors or a marital therapist.

This unsuccessful avoidance strategy suggested that exposure procedures might be more successful. We instructed the patient to abandon attempts to make the pain go away and, instead, to allow the pain to run its course in the setting of medical safety provided by the emergency department. During a subsequent hospital admission he practiced the skill of allowing the pain (and associated thoughts, feelings, and physiologic responses) to resolve successfully on its own, without medical intervention. These repeated trials helped him replace his catastrophic thoughts and maladaptive behaviors with positive coping and self-management skills.

Treatment after discharge focused on setting realistic goals for activities despite his pain and learning to pace those activities. Subsequent care involved problem solving with the patient and his wife to help them decide when to come to the hospital and to clarify the goals of emergency care—for example, obtaining an ECG to check for signs of heart damage versus getting help in controlling chest pain.

Because the patient's symptoms remained unreliable indicators of coronary disease activity, we decided with his cardiologists to schedule exercise testing with myocardial thallium imaging every 6 to 12 months. Thus, we removed the contingency of diagnostic testing on his having continued or increased symptoms.

Marital Counseling

The patient and his wife's alliance was strongly based on their caring for his medical condition. The couple was referred to a marital therapy specialist with the goal of helping the patient manage his pain and his relationships with health care professionals. In 11 sessions during the first year of treatment, the patient became more assertive and the couple developed more effective patterns of communication. His wife became more able to address her concerns regarding conflicts with her teenaged stepchildren.

Treatment Outcome

Health Care Use

The patient first saw us in November 1988. He had 27 hospital admissions in 1988, with 86 inpatient days, including 51 intensive care days (Figure 1). In 1989 he was admitted to the hospital 7 times, with 33 days in the hospital that included 9 intensive care days. The patient's inpatient use continued to decrease over the next three years. The use of parenteral narcotics for chest pain also decreased markedly. Conversely, the number of outpatient visits rose from 6 in 1988 to 50 in 1989 and then gradually declined over the following years. Most of these visits were to us or the marital therapist.

Figure 2 shows that, using standard costs—based on billing rates from local community hospitals—for the number of days in the hospital and in the intensive care unit, procedures, and outpatient visits, the cost of this patient's care went from $134,850 in 1988 to $47,000 in 1989 (a reduction of 65%) to $11,750 in 1990 (a reduction of 91%).

Patient Functioning

At the beginning of treatment, the patient reported that he spent most of his time at home reading or doing crafts projects. His relationship with his wife revolved around his medical concerns. After a year of treatment, the patient and his wife got jobs managing a large apartment complex and, ironically, his admissions to the hospital in the third and fourth years of treatment were for orthopedic procedures for injuries related to painting and heavy yard work.

Discussion

Our report differs from previous ones[21,23] in several important ways. First, our patient had severe coronary artery disease with several recent infarctions. Some physicians and nurses were reluctant to pursue behavioral therapy for a given episode of chest pain in this high-risk patient and instead favored aggressive medical treatment. Our ap-

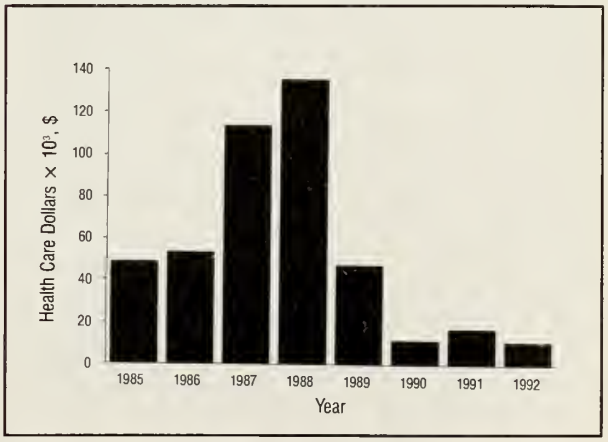

Figure 2.—The patient's annual estimated health care costs are shown. Using standardized costs (see text) for ward and intensive care unit bed days, hospital costs for this patient decreased by 65% in the first and 91% in the second year of treatment.

proach was risky—for example, relying on resting ECG changes to rule out ischemia or infarction during episodes of chest pain. We worked closely with the patient's cardiologists, who accepted this risk given his many evaluations with normal findings and the fact that his previous coronary events were always easy to recognize on an ECG.

Second, our intervention involved taking over the primary medical care of the patient. By consolidating and coordinating his health care, we "treated" the health care system as well as the patient. We were also able to combine medical and behavioral treatments in a way that was acceptable to the patient, while also reducing health care use and costs.

Conclusions that can be drawn from our single case report are clearly limited. The patient's condition may have improved for reasons other than our treatment approach. For example, the patient and his wife relocated during treatment to alter their relationships with some of their children; this move also brought them closer to our hospital. Their decision to move, however, was clearly influenced by their work in our problem-solving and marital therapy sessions. Alternatively, the patient may have had an undiagnosed, self-limiting psychiatric condition such as transient hypochondriasis,[34] hypochondriacal symptoms,[35] or posttraumatic stress disorder[36] in response to his severe myocardial infarctions. Or he may have had panic disorder, major depression, or somatization disorder that affected his symptoms and health care use but failed to reach current diagnostic thresholds.[37-39] He initially received, then discontinued, small doses of imipramine hydrochloride and alprazolam; these medications, along with his behavioral therapy, may have helped treat an unrecognized psychiatric disorder.[40] Although drug and disability seeking were initial diagnostic considerations, they never became important issues in his care.

Successful behavioral therapies for chest pain include reeducating the patient about the meaning of the symptoms; selectively rewarding improved function despite symptoms; self-monitoring of activities and mood; stress management, including anticipating and controlling symptoms with progressive muscle relaxation, biofeedback, breathing retraining, and distraction; physical fitness training; and changing the maladaptive reinforcement behaviors of family members.[21-25] Our combined primary care and behavioral treatment relied on the flexibility and resources of the university-affiliated Department of Veterans Affairs Medical Center and the patient's eligibility for care; as such, it may not be replicable in other settings. Adding mental health services, however, can reduce inappropriate health care costs and use in fee-for-service,[41] military,[42] and managed care[43,44] settings. Future research should be aimed at clarifying ways that primary care and behavioral treatments can be used singly and in combination to treat patients with cardiac and other disproportionate symptoms, disability, and health care use.

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* * *

terminal cancer
last words
"kind man"

Alzheimer's disease
the funeral never ends . . .
I love her

my husband sleeps
for three years now, he's slept—
I want to be held

he stumbles,
eyes blank with memories—
"incoming," he moans

quiet eyes,
final exhalation
distant thunder

exhausted slumber
deathwish waiting for sunrise—
clock's steady ticking

DARYL NIELSEN©
Boulder, Colorado

Commentary

The Doctor-Chaplain Relationship

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As we engage in reform of the health care system in America, relationships among professionals involved in the care of patients become increasingly more important. Decisions about appropriate health care in the light of advance directives, rationing of health resources, and multiple approaches to value-based decisions require open discussion. Chaplains can be an ally and an excellent resource for physicians in a time of making difficult decisions.

Current legislation about advance directives has focused on patients' wishes for care in the final days of life. Yet with expanding technologies and increased success rates of new treatments, physicians and other professionals are faced with more complexity than ever. Family members and guardians and significant others always look for a ray of hope and may be easily swayed to decide for anything that might keep their loved one alive.

In caring for the spiritual needs of a patient, a chaplain may learn the person's depth of faith, beliefs about an afterlife, concerns about the family that will be left behind, and the patient's integration of the meaning of the illness and suffering into life in general. Chaplains often establish a relationship with a patient or family and are involved in conversations about dying. They may have helped draw up an advance directive. All of this information, time, and service can ease transitions and improve the care of patients.

They can be available for the spiritual concerns of physicians, as well. Chaplains have often been advocates for patients and families in taking a stand for a patient being "allowed to die" based on religious beliefs. They have been involved in discussions with patients and families about the benefits and burdens of various treatments. Chaplains have been consulted about the moral implications of stopping or refusing treatment.

This can cause conflict and tension for physicians who do not want to lose a patient or who have one or two more treatments yet to try. This becomes a critical issue especially in large university medical centers when the physician responsible for decisions in a medical crisis is a resident on call or another physician covering for the attending physician. Often these on-call physicians do not know the family and have not been directly involved in the patient's treatment to that point. At times, treatments are described briefly to the patient or family by a physician who then leaves them alone to make a decision.

Chaplains have moved far beyond the days of addressing purely denominational and sacramental concerns or simply offering a friendly visit. Today's certified chaplains are trained in spiritual assessment, sensitivity to all religious faiths and traditions, ethical issues, crisis intervention, and writing advance directives. Although not all have graduated from divinity school, they have participated in supervised Clinical Pastoral Education. Four units of supervised training including 400 hours of seminar and clinical work are required. Certification is awarded after candidates have met standards, have been interviewed by peers or supervisors, and have written documentation in three areas of competence: personal, theological, and professional.

Spiritual care professionals will sometimes be involved in situations where the values and religions of the patients and families differ from their own. Respect for the patient and family and their belief systems is foremost in a chaplain's interventions. At times, referral to a spiritual leader from a patient's own faith is helpful. Chaplains often know persons in the local area who are most willing to help patients who request spiritual care from someone of their own tradition. In some situations, referral to another chaplain may be indicated.

Several strategies have been used successfully to improve the chaplain-doctor relationship. They range from using existing opportunities for discussion to designing new ways to talk about specific concerns.

Chaplains at Saint Louis University Hospital, St Louis, Missouri, for example, have been included as faculty along with physicians, social workers, and nurses in a course on death and dying that is required for medical students. They bring a perspective of spiritual care to the issues discussed.

During the past year, chaplains have coordinated an ethics forum for each service and unit within the hospital. Physicians, social workers, and head nurses were invited to participate, along with a representative from the university's Center for Health Care Ethics. The agenda for the forum was determined by those in attendance, who had been asked in advance to cite ethical concerns of the patients in their care. These were an excellent contact point for chaplains to begin a conversation with physicians.

Another strategy is the chaplain's participation in discharge planning and treatment planning meetings. This

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has increased the number of referrals received by the spiritual care department and is yet another opportunity for dialogue.

Physicians are invited to pastoral care staff meetings to speak about their specialties and to suggest how chaplains may become more involved in the care of patients. Physicians are invited to discuss spiritual issues that patients are facing.

Chaplains were asked to design an individual strategy for soliciting more referrals from the physicians with whom they work. Strategies include calling all physicians in a particular service to discuss referrals, as well as posing specific questions about a particular patient and asking how to be more involved in their spiritual care.

These are some opportunities for partnership with chaplains. Chaplains are a valuable resource in discussions about health care decisions, especially when they have already been involved in the care of a particular patient and family. Chaplains may be allies to support the physician or, at times, advocates for patients who are unable to be heard. Spiritual care brings an invaluable perspective to issues of life and death.

* * *

WISH

I wish I had a waiting room of Georgian women eating yogurt,
ageless Aborigines, the Mabaans of Sudan, the eldest matriarch
of which can hear a thrush at half a mile,

and that, one by one, they would step from the pages
of *National Geographic* to keep their ninetieth annual
routine check-up.

I want to counsel the most ancient Lama of Tibet,
believer of dream time and diets of fish,
"Keep doing whatever it is you do."

But long ago Chauncey Eberhardt, Odell Lamont,
and a tribe of Robert Popes of this world
had drawn me back to reality time.

Odell believes in grizzle and salt.
Chauncey has championed the yet unfilled prescription.
Ten years his junior, in spandex and heels, Mrs. Pope
confesses by proxy, within the flimsy hallway panels,
"While wearing his oxygen, Robert smokes."

I've learned of the strangest rituals and customs
of the tribe of the Robert Popes, how senior statesman Lamont
rules his kingdom with fork and spoon.

No wonder I listen for zebra hooves in between answering calls.
No wonder I imagine my fantasy patient:
an Aboriginal octogenarian, returned from hunting kangaroo,
offers his painted boomerang to partially pay his deductible.

PHILLIP J. COZZI, MD©
Brookfield, Illinois

Commentary

Toxic Intern Syndrome

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I made a promise to myself during medical school that it would not happen to me. My first priority would be patient care and my patients' well-being. I would treat them with respect and dignity. I was determined not to become inured to patients' requests and their pain, as had occurred with many of the interns and residents before me. I do not know exactly when it began, but I soon succumbed to "toxic intern syndrome."

The affliction was pointed out to me by a close friend who informed me midway through my intern year that he no longer wanted me as his physician. I had changed. The process was gradual, occurring over time, and was probably the result of coping with the reality and daily hassles of residency. The naïvete and compassion that I had as a medical student had been replaced by the ennui and callousness of a toxic intern. But I was not unique. Talking to other interns revealed that I was not the only one changing. I stepped back to examine what was happening.

The duration, severity, and onset of the syndrome are highly variable. Some interns contract it earlier in the year, some later, and others presumably exhibit immunity. It is difficult to predict whom or when it will hit or how long it will last.

The signs and symptoms also vary. The signs are expressions of fatigue—slumped shoulders, nodding off during meetings, and perpetual dark circles under the eyes. Irritability mixed with anger is a common symptom. Another is recurrent irritation with support staff, residents, attending physicians, consultants, patients, and hospital systems or the Department of Veterans Affairs (VA). Depending on the duration of the irritating stimulus or the cumulative effects of multiple aggravating situations, this can create irrational and illogical behavior. The behavior frequently manifests in the form of "scapegoating" (yelling at the wrong nurse for an order not completed or blaming them for the intern's own omission), venting anger at a staff member or technician who had nothing to do with the original problem, or raising his or her voice in frustration to patients. Scapegoating is also used against friends, family, and loved ones as the toxic intern takes frustrations from work out on someone at home who has no control or influence over any of it.

The symptoms can occur in a passive-aggressive form, such as striking back at residents, nurses, and patients. Typically they involve an order or test inadvertently "forgotten." Or they may occur as a slow response to nurses for ridiculous crosscover calls. Or a patient may be allowed to leave the hospital against medical advice with no attempt made to persuade the patient to stay.

A pervasive cynicism develops as another means of coping. By now the emphasis has shifted from helping others to conserving energy and managing time efficiently. This is evident in the language used. Patients are viewed as "hits," and residents complain about getting "slammed" on call with admissions. Patients may be checked out as being "stable," only to "go bad" soon after their team is out of the hospital. The "dumps" take on many forms. The chronic-care or nursing home patient is "dumped off" before long weekends to become the responsibility of the hospital. Patients can also be "dumped" within departments, from one service to another and from one hospital to another. The classic example is the male veteran who is emergently transferred to the VA hospital once a military service record is established. Patients are described as "wimps," "drug-seekers," "gomers," and "worthless scum."

Survival becomes a peculiar game, one that frequently neglects patients' best interests. The goal is not to admit patients, but rather to "bounce" or "turf" them to other services, to reject transfers, and to immediately discharge when a patient's condition becomes stable. The game may necessitate coercing other departments into providing the consultation or needed tests. On weekends or after hours at the VA hospital, it means relying on hope and prayer that patients will not get sick, because it requires even more than the normal hassle to get basic laboratory or x-ray tests done.

The cause of the syndrome is relatively clear—too much "scut" work (some common unfinished task), too little pay, and too many hours spent in the hospital. The hours are frequently spent dealing with patients' social issues rather than medical illnesses. Nursing home candidates cannot be placed because of lack of funding or "undesirable characteristics," so they stay until a nosocomial infection occurs, necessitating an even longer stay in the hospital. Alcoholic patients initially present with massive gastrointestinal bleeding, are transfused, treated, and released, only to return bleeding again after yet another drinking binge. Gang members are admitted with gunshot wounds after an altercation; rival members must be sepa-

(Dyer KA: Toxic intern syndrome. West J Med 1994; 160:378-379)

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rated in the hospital and visitors carefully monitored. Intravenous drug injectors present with skin-popping abscesses demanding high doses of pain medication for minor dressing changes or develop a new heart murmur or endocarditis, buying a six-week in-house course of intravenous antibiotics.

By this time the syndrome has taken its toll. Now the toxic intern forces patients to walk on postoperative day one and listens to intravenous drug injectors and patients with gunshot or stab wounds complain without increasing their pain medication. (The downside to this is that suddenly everyone is suspected of drug-seeking behavior.) The toxic intern will interrupt patients during long, rambling historical recounts, forcing them to get to the point. The intern becomes oblivious to pain elicited during procedures, while incising and draining drug-induced abscesses, during lumbar punctures or paracenteses, and while placing central venous lines. Disability benefits are denied to those wanting them for back pain, gunshot wounds, or obesity. The toxic intern gradually resents the sense of entitlement found in many medicaid patients who want everything done, but who are frequently the most noncompliant and have contributed little for their medical treatment.

Unfortunately there may not be a cure, short of stopping the toxic impulses before they occur. Once a person becomes infected with the toxic intern syndrome, she or he is never the same. It becomes a strong coping mechanism for internship and residency, providing interns with the ability to turn off their emotions. Survival, not patient care, becomes the first priority. There are periods of exacerbation and remission during residency that usually subside once a person enters private practice. For those who stay in academia, there is the protective effect of being an attending physician, keeping them insulated from daily problems, and allowing them to remain relatively free of symptoms.

The only effective treatment is prevention. This would require restructuring much of the current health care system. Medicaid, medicare, health care for the indigent and illegal aliens, and insurance programs would all need to be revised into a more user-friendly system, one less susceptible to misuse and abuse. It would also require revamping residency programs, limiting work hours, and creating a pay scale with benefits (an unlikely event because of the cost).

The frustration of trying to cope with daily battles, coupled with constant stress and fatigue, eventually leads to resignation, the realization that the system will not change, and finally complacency. The ultimate coping mechanism is to just sit back, relax, and take it. It is easier than constantly fighting. The toxic intern can only hope that recurrences are short-lived and that patients, in the long run, do not suffer too much.

Editorials

Future Trends in the Incidence and Management of Prostate Cancer

The management of prostatic diseases has received considerable attention in both the scientific and lay press over the past five years. Once the domain of urologists, prostatic hyperplasia and carcinoma have now become diseases of interest to primary care physicians, oncologists, endocrinologists, epidemiologists, public health officials, talk show hosts, and television anchorpersons. Histologic evidence of benign hyperplasia is nearly ubiquitous among America's elderly men, with roughly 40 million men at risk for voiding dysfunction and morbidity from the disease. Histologic evidence of prostatic carcinoma is frighteningly common, with about 30% of all men older than 60 showing carcinoma, as reported in several autopsy series. A recent autopsy study of young trauma victims (aged 39 years or younger) revealed that 33% of men in the 30- to 39-year age group had microscopic evidence of prostatic carcinoma on careful examination of the gland. Whether "clinically significant" prostate cancer would have developed in these men in their lifetime is unknown; nevertheless, the study findings underscored both the high prevalence of histologically detectable prostate cancer and the often latent nature of this unusual malignant disorder. Although the prevalence of prostatic carcinoma is difficult to define, more than 25 million men are estimated to have occult prostatic carcinoma. With staggering numbers such as these, it is easy to understand why interest in prostatic diseases has spread to nonurologists.

The medical and economic effects of prostatic diseases promise to become even more serious in the next 20 years, as the men born in the post-World War II era (the "baby-boomers") reach the age when prostatic disease becomes manifest. The treatment of prostatic hyperplasia and carcinoma already consumes a substantial percentage of the Medicare and general health care budget—with estimates of as high as $1 billion spent annually in direct and indirect costs. At the present rate of rise in the incidence of clinically significant prostatic carcinoma (macroscopic or biochemically detectable cancer), by the year 2000 more than 200,000 cases will be diagnosed each year in the United States. The overwhelming majority of men with this diagnosis are vigorous and healthy and would warrant either curative (radical surgery or irradiation) or palliative therapy. At a conservative cost estimate of $10,000 to $20,000 per case diagnosed for either curative therapy or lifetime palliative care, the annual cost for prostate cancer alone could soon approach $2 billion to $4 billion. In an era of medical fiscal constraints, these increases would be unacceptably burdensome.

The well-written treatise on hormonal therapy for metastatic prostate cancer by Marko Gudziak, MD, and Anthony Smith, MD, elsewhere in this issue of the journal covers the rationale for hormonal ablation of systemic prostate cancer in complete detail.[1] Among the most important elements of this work is the cost analysis contained in their Table 3. Orchiectomy is the most cost-effective means of managing disseminated prostate cancer. Unfortunately, when given a choice between surgical (orchiectomy) and medical (luteinizing hormone-releasing hormone [LH-RH] analogue) castration, most men (roughly 80%) choose the more expensive option—medical hormonal ablation. In the present social climate, it is unlikely that men will be denied their choice of medical therapy with an LH-RH analogue (leuprolide or goserelin). Thus, a minimum cost of $10,000 can be expected for treating a case of metastatic prostate cancer over the patient's lifetime.

A growing wealth of evidence also supports the use of the antiandrogen flutamide (Eulexin) in an effort to neutralize androgens of adrenal origin, which have been shown to stimulate prostate cancer growth. In most trials, adding an antiandrogen has meant a survival advantage of 6 to 19 months for most men taking the drug, along with some form of castration. Patients with poor prognostic indicators and a poor performance status do not benefit from combined androgen blockade, so antiandrogen therapy should not be used in these men. This group is a minority, so cost savings from this approach would be minimal. Thus, an additional $5,000 expense can be expected from treating incurable cancer. When coupled with the cost of castration, the treatment of disseminated prostate cancer approaches $8,000 to $15,000 per case. These figures exclude the costs of diagnosing and monitoring the disease and of treating patients in their final 6 to 12 months of life when the cancer develops resistance to hormonal deprivation.

Clearly, treating prostate cancer in its most advanced stages is an expensive proposition. The cost of potentially curative therapy is likewise appreciable. The cost of radiation therapy and radical prostatectomy varies regionally, but is in the range of $10,000 to $15,000. Naturally, for some men localized therapy will fail, and they will require treatment of systemic disease; others may suffer complications from radiation or surgical therapy with their attendant costs. Although a novel, minimally invasive approach to local treatment—cryosurgical ablation of the prostate—offers the possibility of an effective treatment of localized disease in, possibly, an outpatient setting, greater experience will be needed with this technique before it can be considered effective in curing or controlling cancer. The cost of cryotherapy could be less than that of radical surgery—with the obligate four- to seven-day inpatient stay for a major operation, and also less expensive than 70 Gy of external irradiation. Even with more efficiently delivered care of localized prostate cancer, the cost of treating prostatic cancer with present methods is substantial.

Current research into prostate cancer treatment includes outcome analysis whereby the efficacy, morbidity, and cost of competing modalities are compared. Because

of the indolent nature of many cases of prostate cancer, the benefits and risks of deferred treatment—or even no treatment at all—must be compared with those of aggressive management. In this country, we are already seeing the benefits of public education about healthier lifestyles. Dietary modification, smoking cessation, daily exercise, safer homes and highways, and better medical care—especially cardiac and hypertensive care—will all contribute to a greater longevity for American men. Although prostate cancer will not present a mortal threat to every man who is diagnosed with the disease, morbidity from localized and disseminated disease is considerable and costly. As American men live longer, the potential for morbidity from localized tumor progression or advancing systemic disease will increase, and the expense of treating more advanced disease will be substantial. Although active observation of patients with prostate cancer with deferred treatment has its proponents, this may end up being an expensive experiment as men in excellent general health require many treatments to palliate for advancing cancer. Our hope is that carefully designed prospective studies incorporating outcomes research tools will soon yield solutions to these vexing issues.

In the basic and clinical research areas, however, rests the future of prostate cancer management. A nationwide prostate cancer prevention trial is currently accruing men in a seven-year experiment to determine whether the drug finasteride (Proscar), an inhibitor of the potent androgen, dihydrotestosterone, is effective in preventing prostate cancer development. This randomized, prospective, placebo-controlled and double-blind trial has sparked considerable controversy because the chemopreventive abilities of finasteride are still to be proved. But it offers some hope of stemming the tide of the onrushing prostate cancer "epidemic."

Epidemiologic studies have recently linked dietary fat and cholesterol intake to prostate cancer occurrence. With changes in American dietary habits, the incidence of prostate cancer may stabilize as Americans consume less dietary fat. In a related finding, levels of vitamin D, both from dietary intake and from ultraviolet sources, may promote prostatic carcinogenesis. Lifestyle changes eliminating either of these risks may lower the prostate cancer risk.

Finally, genetic-linkage analysis techniques are being used in cases of familial prostate cancer in hopes of identifying regions of the genome responsible for the initiation or promotion of prostate cancer. If genetically engineered tumor suppressor regions can be inserted into the host genome, prostatic carcinogenesis can be interrupted in its earliest stages—if not prevented altogether. Although these research efforts are expensive, the possible future benefits must be considered in light of the increasing incidence of prostate cancer, increasing costs of treating the disease, and shrinking health care funds available. Although current treatment modalities may be satisfying to those who treat prostate cancer patients, we must recognize that these methods will become increasingly costly at a time when costs must decline. In innovative basic science laboratories around the country, research in breakthrough technologies offers the only hope for gaining control of this disease.

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Moles and Melanoma—New Method in the Madness

SINCE THE INITIAL histologic recognition of melanocytic nevi ("moles") and cutaneous malignant melanoma, a poorly understood relationship between these two disorders has persisted to this day.[1-3] Although melanocytic neoplasia is the focus of increasing research, fundamental knowledge concerning it remains limited but has nonetheless provoked considerable controversy and debate. Both nevi and melanoma seem to be inextricably linked because of the common clinical history of an antecedent nevus at the site of melanoma (reports vary from 19% to 85%), the histologic contiguity of nevi with melanoma (estimates range from 18% to 72%), and the observation that melanoma patients often have numerous, unusual, or "funny" nevi.[1] Because of the rapidly increasing incidence of cutaneous malignant melanoma among white populations worldwide in recent years and the recognition that melanocytic nevi (both typical and atypical) are in fact important risk factors for cutaneous melanoma, there are compelling reasons to better understand this curious relationship.

Given the importance of the relationship between nevi and melanoma, it is surprising how little has been known until recently about melanocytic nevi. What are the origin and nature of these peculiar growths? It seems clear that nevi originate from cells migrating from the neural crest to the skin.[1-3] The immediate origin of nevi seems to be the proliferation of intraepidermal melanocytes, the subsequent migration into the dermis, and terminal differentiation. An alternative hypothesis is that these migratory cells from the neural crest may reach the dermis as nerve sheath-associated cells, with the epidermis as the final destination and place of terminal differentiation.[4] Irrespective of the sequence of nevus development, little is known concerning the mechanisms of proliferation, cell migration, and differentiation in nevi.

Because melanocytic nevi are not considered normal structures, there has been a long-standing debate as to whether they are hamartomatous or neoplastic.[2,3] Nevi present at birth—congenital nevi, particularly giant varieties—probably are hamartomatous. On the other hand, there is also mounting evidence from experiments that melanocytic nevi in general are indeed neoplastic and are lesions intermediate in the tumor progression of melanocytes to melanoma.[5-12] The cells that make up nevi have been called "nevus cells" historically. These cells differ from basilar intraepidermal melanocytes because of their

aggregation in syncytial nests, general lack of dendrites, and slightly larger size compared with basilar melanocytes.[2] Nevus cells show cytologic and ultrastructural features in common with basilar melanocytes, and various authors have eschewed the term "nevus cell."[2]

Nomenclature aside, nevus cells do show considerable differences from normal melanocytes.[5-11] Compared with the growth requirement of normal melanocytes, nevus cells (and melanoma cells) placed in culture do not require stimulation by the growth promoter, 12-*O*-tetradecanoyl-phorbol-13-acetate.[6,11] Similarly, both nevus cells and melanoma cells show anchorage-independent growth in soft agar as opposed to the lack of this property by normal melanocytes. Nevus cells also differ from cultured melanocytes in other respects. Melanocytes have predictable growth properties in culture compared with the substantial heterogeneity of nevus cells. In common with melanoma cells in culture, nevus cells produce basic fibroblast growth factor, as evidenced by both protein and messenger RNA expression, whereas normal melanocytes do not.[11]

When normal melanocytes, nevus cells, and melanoma cells are examined for the expression of various cell surface antigens, nevi tend to show a pattern intermediate between normal melanocytes and melanoma.[6-9] For example, certain cell surface antigens are expressed at a much higher frequency by nevus cells than by normal melanocytes.[6-9] In addition, it has been shown that there may be considerable overlap in the expression of certain antigens by nevus cells and melanoma in the radial growth phase.[8] These various studies strongly support the idea that melanocytic nevi are neoplastic and a step closer to melanoma than normal melanocytes.

The dysplastic nevus—nevus with architectural disorder, cytologic atypia, or both—a lesion occupying a middle ground between ordinary nevi and melanoma and thought to be only one step away from cutaneous malignant melanoma, has received an inordinate amount of scrutiny and discussion.[10,12] The reasons for the *Sturm und Drang* (and perhaps madness) surrounding dysplastic nevi have been related to issues of nomenclature and also to the inability to articulate clearly the upper and lower limits of this disorder in relation to ordinary nevi on the one hand and radial growth phase melanoma on the other.[12] In fact, the latter exercise may be exceedingly difficult because melanocytic dysplasia is probably a continuum and not subject to easy categorization. Most observers would agree that there is a range of clinical and histologic abnormality that is clearly separable from ordinary nevi and melanoma such that dysplastic nevi do represent an intermediate phase of tumor progression.[12]

The legitimacy of dysplastic or atypical nevi has been substantiated by a body of clinical and experimental information.[7-10,12] Dysplastic nevi are in general grossly larger—4 to 12 mm or more—than ordinary nevi. They show an intermediate range of color and border variation and finally an intermediate degree of both architectural and cytologic abnormality histopathologically.[12,13] As discussed earlier, dysplastic nevi also tend to express melanocyte-associated antigens such as HLA-DR, epidermal growth factor receptor, nerve growth factor receptor, and gangliosides, intermediate between ordinary nevi and melanoma.[12] They also tend to have a higher frequency of random chromosomal abnormalities compared with ordinary nevi, but not the nonrandom chromosomal alterations observed in melanoma.[6] It has also been noted that dysplastic nevi with high-grade atypia show a substantially greater mean nuclear area of intraepidermal melanocytes compared with nevi with lesser degrees of atypia as evidenced by image analysis.[14] Furthermore, dysplastic nevi tend to show an intermediate spectrum of abnormal DNA content of melanocytic nuclei relative to ordinary nevi and melanoma. In general, recent studies have documented a trend of increasingly abnormal DNA content that parallels the degree of melanocytic cytologic atypia—slight, moderate, or severe—in dysplastic nevi.[15] All of these various sources of information again support the idea that dysplastic nevi occupy an intermediate stage of tumor progression between common nevi and malignant melanoma.[12]

If melanocytic nevi, especially dysplastic nevi, are possible precursors to melanoma, why are nevus remnants in general found with such low frequency (~30%) in cutaneous malignant melanoma? Or, stated differently, why do about 70% or so of melanomas apparently develop de novo, without evidence of a nevus?[16] First, as mentioned earlier, virtually all cutaneous malignant melanomas develop from a proliferation of intraepidermal (often basilar) melanocytes, irrespective of whether a nevus remnant is present or absent. Differences in the pathogenesis of the various subtypes of cutaneous melanoma could partly be related to the extent to which they originate from nevi. For example, approximately 3% of lentigo maligna melanomas, few acral lentiginous melanomas, 6% of nodular melanomas, and 30% or so of superficial spreading melanomas have contiguous nevi.[16] The frequency with which nevus remnants are detected could be influenced by the extent of sampling (less sampling would yield lower prevalence), tumor progression of the nevus itself, obliteration of the nevus by melanoma, and the inability to distinguish an atypical precursor from melanoma. The last circumstance has remained a serious problem because the peripheral (usually intraepidermal) portions of some or many melanomas may exhibit less atypia and thus be confused with a precursor. Without a definite marker, it may not be possible to distinguish a precursor, and thus this would affect the frequency with which "dysplastic" precursors are identified.[16]

As reviewed by Williams and Sagebiel in this issue of the journal,[17] melanocytic nevi are among the leading risk factors for cutaneous malignant melanoma, regardless of their precursor status. A number of studies have established a significant correlation between various indicators of nevi and melanoma risk. For example, the total number of ordinary nevi on the skin surface, number of nevi on various anatomic regions, such as the arms or trunk, and estimates of total nevus density—a variable derived from both number and size of nevi[18]—have all been linked with

increased melanoma risk. Various features of clinically atypical or dysplastic nevi — >5 mm, irregular or ill-defined borders, haphazard or variegated color—have also been shown to independently predict melanoma risk as both continuous and dichotomous variables. Because of the difficulty in arriving at the minimum criteria for an atypical or dysplastic nevus or atypical nevus phenotype, estimates of melanoma risk have varied from study to study.[12,17]

Taking a practical approach, we have studied the melanoma risk in 155 patients judged to have nevi atypical enough to require regular clinical examinations in the years between 1980 and 1985.[19] The risk of invasive melanoma in this population was found to be threefold greater than in controls. In this same patient group, in addition to the 2 persons in whom invasive melanoma developed, 23 had at least one nevus removed that was described histologically as severely atypical. Because some dermatopathologists would designate some or many of such lesions as melanoma in situ, the extremity of melanoma risk in these patients seems beyond dispute. Other studies have yielded similar results and emphasize that an abnormal mole phenotype, irrespective of histologic features, is an important risk factor for melanoma.[12,17,20,21] In fact, a recent study examining histologic melanocytic dysplasia alone failed to show any clear correlation with increased melanoma risk.[21] It is possible that melanoma risk might be related to a certain threshold of melanocytic atypia, such as high-grade cytologic atypia.[12]

As further discussed by Williams and Sagebiel, various formulations have been proposed to estimate melanoma risk in patients by assessing risk factors for melanoma that have been validated in case-control studies.[17] In addition to total number of nevi and the presence of clinically atypical nevi, other important variables include a family history of melanoma (especially in first-degree blood relatives), a family history of numerous or atypical nevi, a personal history of melanoma, and the presence of immunosuppression. A synthesis of these various studies suggests that melanoma risk directly correlates with the last variables in a dose-response manner. Although the phenotypic expression of these variables is almost certainly a continuum, attempts have been made to stratify patients into groups with differing degrees of melanoma risk.

MacKie and colleagues recently reported that the melanoma risk in patients with clinically atypical nevi but no personal or family history of melanoma was the same as in comparable patients with a personal (but no family) history of melanoma (relative risks 92 and 91, respectively).[21] A much higher melanoma risk (relative risk 444) was noted in patients with clinically atypical nevi and a family history of melanoma, in contrast to the other two groups. Differences in melanoma risk among various studies analyzing these various subsets are likely to be due to differing criteria for atypical nevi and phenotypes, differences in study populations, number of study subjects, and heterogeneity. A consistent conclusion from such studies is that the highest melanoma risk is found in individuals within familial melanoma-atypical mole kindreds.

Because of the importance of both physicians and health care professionals recognizing such high-risk persons, Williams and Sagebiel have outlined general criteria for normal versus abnormal mole patterns.[17] Despite remarkable heterogeneity of nevus patterns and corresponding melanoma risk, providing such guidelines is a useful first step for the evaluation of patients with prominent nevus phenotypes. Most "normal" persons have fewer than 25 nevi, and their nevi usually measure less than 5 mm in diameter and have uniform pigmentation and regular and well-defined borders. On the other hand, persons with more than 50 nevi or those with larger and more variable nevi are defined as having an abnormal phenotype. They should be questioned as to personal and family histories of melanoma and ideally first-degree blood relatives examined for an abnormal nevus phenotype. Once this "staging" has been done, patients and family members (if applicable) should undergo periodic skin examinations for the possible detection of early melanoma, according to a standardized protocol similar or identical to the one outlined by Williams and Sagebiel.[17]

The application of more quantitative methods to assess nevus phenotypic characteristics described in this issue[17] and in recent studies should facilitate a more rigorous estimation of melanoma risks.[23] The method described by Kenet and co-workers involves examining a nevus covered with oil (or another suitable agent) with low magnification and capturing a digital image of the nevus for further analysis and future comparison. Although not suitable for routine primary care practice at this time, such methods hold promise for identifying high-risk precursors or early melanoma.

Thus, despite insufficient knowledge about many aspects of melanocytic neoplasia, new information continues to emerge, such as the importance of recognizing an abnormal mole pattern on clinical examination. Such information is of great practical value for identifying persons at increased risk for melanoma and their need for periodic follow-up examinations.

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Lessons From the Practice

What's His Code Status?

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The intensive care unit (ICU) was alive with the sounds of dying: from Room 1 came the sobs of relatives encircling a loved one; from Room 3, the mournful sighs of the ventilator blew against a pair of stiff, weary lungs. As the new intern, I was in the center of the din, writing admission orders, following medical school mnemonics. My beeper went off.

It was my resident, summoning me to the emergency department, "stat." I arrived to see a 90-year-old husk of a man, on his back, struggling with his six caretakers who were desperately trying to insert tubes into his arteries, veins, bladder, and throat.

"Acute respiratory distress secondary to food aspiration," my resident informed me. "You're looking at a dead man," pointing out the livedo reticularis. "Hey, what's this guy's code status?" From a corner, someone responded, "I've got his private doc on the phone. He's a no-code, no-intubation." At that moment, the physician at the head of the table murmured, "I can see his cords. I'm goin' in . . . ," and the endotracheal tube was inserted. "You guys can settle this one in the Unit. I'm just doin' my job."

And so, in time, to the ICU we rolled. "Get weaning parameters on this guy," the resident ordered me. "If we can get him off the vent, we will, and then if he codes we won't reintubate." After scanning the old records, he continued, "This Mr Gilman is a frequent flier, a stomach cancer-GI bleeder who comes in monthly for blood. He's so gorked he doesn't know where he is. Anyway, I'll get the private to initial a DNR order, and we'll be covered." And off he went to see another new admission.

I introduced myself to Mr Gilman over the clamor of the respirator and told him where he was and what was happening to him (though I was not so sure, myself). Before I knew it, the door to the unit swung open and in swarmed the relatives, weeping in their native language. They engulfed the patient with their concern, identifying the sunken orbital fossae and blue lips as "Daddy." A puffy-faced woman grabbed my arm. "Are you taking care of my father?" she cried. "Oh, please do everything for him. He's my whole life, the patriarch of our family."

I looked at the patriarch—hollowed cheeks, wasted limbs, chest inflating rhythmically on mechanical command, arms restrained with intravenous lines. What did he want, I wondered. Did his tear-ravaged daughter, who laid claim to his affections, represent his desires?

His wishes were irrelevant as far as Mr Gilman's children were concerned. "He doesn't even know he has cancer; we didn't want to upset him," they whispered. "Look, we don't care what you have to do to Daddy; we want him alive!" was the command.

I carried their request to my resident, who relayed it to the fellow, who deposited it in the lap of the private attending physician. The last was piqued that a particularly ardent daughter was "manipulating" the rest of her siblings, who, the attending insisted, had given him distinct verbal agreement to a "no code status" after Mr Gilman's previous hospital admission.

What to do? Gratify the wishes of the next of kin? Their un-self-consciously selfish statements appalled us. Their assumption of authority intimidated us. Mr Gilman moaned and pointed to his abdomen, but did not respond to questions. Over the days that followed, he required obtunding doses of narcotics to remain "comfortable." Perhaps because of these respiratory depressants, he could not be weaned from the ventilator during a week of daily attempts. The family, suspicious of our intentions, accused the medical team of pushing him too fast.

What to do? Leave Mr Gilman indefinitely in the ICU with ventilator and morphine drip as constant companions? Ask the family for "permission" to take their father off the ventilator? Decrease the dose of medication long enough to demonstrate his pain graphically—and appeal to the family's humane instincts while violating our own?

We called a meeting. Our goal was to obtain family consent for an official "no code status" on the chart. This was to end our dilemmas, both medical and legal. Or would it?

The conference room crackled with animosity and distrust. The fellow opened the discussion with his indignation: How dare the family insinuate that he, a physician, wanted their father dead? Aren't we all on the same team? he rebuked them. The family's initial hostility was quickly transformed into pitiable deference as they perceived the danger of antagonizing the white-coated tribunal that confronted them. Perhaps a show of vulnerability and doctor-worship would be better strategies to use to save their father.

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The children's guilt spilt from tremulous lips: Mr Gilman was being spoon-fed by them when he aspirated. Would his death now be a result of their actions? Although they recognized it might be in his "best interest" to die after so much suffering, they were unable to let go. They could not remove him from the ventilator. We were asking them to sign his death sentence.

As the preceding vignette demonstrates, the pursuit of code status, far from being a panacea for medical dilemmas, raises a panoply of its own ethical and moral questions. Who should be charged with making decisions about the aggressiveness of medical care if the patient's wishes are unobtainable? Do past directives supersede current choices? Are family members the proper surrogates, or do we ask them to play God when they are the most stressed?

The children of Mr Gilman were in obvious turmoil from the moment they set foot in the ICU; their insistence on "doing everything" may have stemmed from their sense of culpability or possibly other family dynamics unknown to the medical team. Subsequently, they felt they were being pressured to sanction the death of their loved one, rather than simply to wean him from the ventilator if he were ready.

Is it appropriate to begin, and once begun, to continue, life-sustaining technologic measures for every patient who cannot express his or her wishes? Mr Gilman suffers so much that he must be made comatose to be pain-free. Is it unreasonably paternalistic for a physician to decide that, if respiratory failure recurs after weaning, further mechanical intervention should be withheld?

Some clinicians contend that humanistic issues can be approached in a systematic fashion, much as we develop algorithms for managing arrhythmias. They urge the establishment of "criteria" or advance directives to help simplify our task.

Indeed, it may be tempting to leapfrog over the emotional particularities of each patient's terminal situation and embrace the physician's role as automatic life-prolonger, duty-bound to apply artificial life support unless expressly forbidden by living wills, durable powers of attorney, or countersigned no-code-blue orders. But helping patients and their families confront their mortality may require more "art of medicine" than such protocols can anticipate.

The blind pursuit of code status orders is becoming routine. "Full code" is every patient's entitlement and every physician's duty, unless explicity ordered otherwise. As the struggle over Mr Gilman's fate illustrates, humane medical care requires a more nuanced choice of options than a preselected code or no-code status can afford.

Mr Gilman survived the ICU. He was weaned off the ventilator, transfused three units, transferred out of the ICU, and lost to my follow-up.

Flatline

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The headline read, "Homicides in 1992 Set Record for L.A. County." Gang warfare, civil unrest, proliferation of lethal weapons, and despair converge to blacken the stain on this troubled region. Murder is a fistfight with guns, someone said. Pulling the trigger is easier than breaking your bones on someone else's face. Now that the new year has risen from the ashes of the last and the final scorecard is in, we can look back on 1992 and consider the 2,589 dead bodies as a monument to evil and yet another victory for a dark force that inexorably crushes the conscience of the human race. We are surely doomed to repeat, and probably to surpass, the slaughter of 1992 for the simple fact that we are no longer shocked by violence on this scale. After all, nearly 2,600 homicides is just a number, a single clump of bodies whose individual outlines are indistinct.

But what if somehow all of us could focus on each one of these murders, dissect each person away from the cold statistics, and put the long tendrils of pain under a microscope, look at the details of each one, and stare at the syncytium of anguish and loss? What if we could see the faces of the parents, classmates, friends, of all the people touched in their singular way by the violent death of each solitary victim? The numbers would then turn blood red; we would have to turn our faces away from the ghastly horror of the gunshot wounds, the severed necks, the beaten mass that had once been human with a family, friends and lovers, and, perhaps, with a hope that the future would not be as grim as this last day. Chairing an ethics subcommittee showed me the faces close up.

I was introduced to Sandra and met her devoted parents and grandparents. I was told she had been popular at school, with lots of friends and four younger sisters who looked up to her. The family just happened to live in a part of town infested with gangs. One day, over two years earlier, Sandra had been driving with friends through the neighborhood when a car appeared out of nowhere, screeching around the corner, gunfire blitzing out of the

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From the Laboratory, Pomona Valley Medical Center, Pomona, California.
Reprints not available.

windows. A bullet went through the trunk of the car Sandra was in and got her in the back of the head, lodging in her brain stem.

Close to death, she was rushed by paramedics to a local hospital where she was stabilized but comatose. After the acute episode, she was transferred to an extended care facility where until recently she remained in a persistent vegetative state. Her parents visited her daily, believing each time that Sandra was giving them some sign that she knew they were there. They clutched the memory of Sandra when she was not rigidly contracted, with bubbles of secretions gurgling out of her tracheostomy tube and some thick, foreign-looking potion sludging into her through a gastrostomy tube.

I saw the father in the hall one day, a week after Sandra was transferred to my hospital in septic shock. He was a small man with dark hair sprinkled with gray and lines of vigilant worry carved around his eyes. Sandra was now on a ventilator in the intensive care unit, brain dead. The father had wanted her taken off the ventilator as soon as the neurologist told him that Sandra's brain function was nearly gone. The ethics subcommittee deliberated over the parents' request, concerned about the legal issues of the bullet in Sandra's brain and what some unseen defense attorney might have to say. All of us knew it was right to support the parents' wish to see the end of their daughter's suffering; we also knew that it was not Sandra who was suffering, but they. Parents should not be witness to the death of their child.

Two years is a long time, we were told by Sandra's parents, who thought their tears had dried long ago, but whose anger was kept smoldering by what they also saw as a pervasive and wanton disregard for human life. Two long years had passed, each day spent watching a daughter's vacant eyes reveal the loneliness of the dying, knowing she will never again jump into your arms and kiss you, knowing that at some point you must say good-bye forever. The father was waiting for the organ procurement agency to determine whether Sandra's organs could be donated for someone else's use. He desperately wanted to know that part of his daughter was alive somewhere.

This, I know, is not an unusual story. I also know that there are stories more tragic, if tragedy on this scale can be quantified. To think that this happened 2,600 times in 1992 shatters my thoughts; it is like contemplating the possibility that Hell has clawed its way to the surface. We can pretend that in Los Angeles this is not genocide, that the brutality in Bosnia-Herzegovina is the raw distillate of the devil's passion, that here in our urban war zones it is a natural process because of the nature of the people who live there. The media publish pictures of the dead in other countries; why not do the same from the sterile corridors of the county morgue? Let our photojournalists anger us about each of the 2,600; make us weep that just a few miles from where we live lies a misshapen corpse that leaves a family bereft. Show us the close-ups. Show us, sensitively and with the virtue of compassion, the families huddled with heads turned down, weakened by the loss of a loved one; show us the pictures that will make our species unite against this virus of self-destruction. Our society does not have to be another Belshazzar on the verge of defeat.

I walked up to the intensive care unit later that last day. It still had not been decided if Sandra's organs could be used. I went to her room to look in on her. On the far side of her room, hunched into a small, curved form, was her father, holding one of his daughter's contracted hands. His body shook as tears glistened in his eyes.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

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In Memoriam

California Medical Association

Clapper, Jack W., San Bernardino. Died Jan 5, 1994, aged 79. Graduate of University of Kansas School of Medicine, Lawrence, 1948. Licensed in California in 1953. Dr Clapper was a member of the San Bernardino County Medical Society.

Clement, Eugene D., Castro Valley. Died Jan 1994, aged 73. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1946. Licensed in California in 1946. Dr Clement was a member of the Alameda-Contra Costa Medical Association.

Conley, Edward, Modesto. Died Oct 13, 1993, aged 49. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1969. Licensed in California in 1969. Dr Conley was a member of the Stanislaus Medical Society.

Degnan, George, Martinez. Died Feb 4, 1994, aged 80. Graduate of McGill University Faculty of Medicine, Montreal, 1939. Licensed in California in 1939. Dr Degnan was a member of the Alameda-Contra Costa Medical Association.

Gericke, Otto Luke, Patton. Died Jan 20, 1994, aged 86. Graduate of University of California, San Francisco, School of Medicine, 1933. Licensed in California in 1933. Dr Gericke was a member of the San Bernardino County Medical Society.

Gleckler, William H., San Mateo. Died Jan 1994, aged 73. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1944. Licensed in California in 1950. Dr Gleckler was a member of the San Mateo County Medical Association.

Godwin, J. David, La Jolla. Died Jan 1994, aged 84. Graduate of Indiana University School of Medicine, Indianapolis, 1942. Licensed in California in 1948. Dr Godwin was a member of the San Diego County Medical Society.

Gordon-Kampf, Susan U., San Marcos. Died Dec 1993, aged 58. Graduate of Lekarska Fakulta Palackeho Univerzita, Lidicka, 1962. Licensed in California in 1948. Dr Gordon-Kampt was a member of the San Diego County Medical Society.

Grow, Kenneth A., Palm Springs. Died Oct 29, 1993, aged 80. Graduate of Indiana University School of Medicine, Indianapolis, 1950. Licensed in California in 1950. Dr Grow was a member of the Riverside County Medical Society.

Hahn, Eugene A., Sacramento. Died Jan 19, 1994, aged 78. Graduate of Hahnemann Medical College, Philadelphia, Pennsylvania, 1945. Licensed in California in 1948. Dr Hahn was a member of the Sacramento-El Dorado Medical Society.

Kemalyan, Arthur A., Lodi. Died Feb 3, 1994, aged 64. Graduate of Baylor College of Medicine, Houston, 1960. Licensed in California in 1961. Dr Kemalyan was a member of the San Joaquin County Medical Society.

Kennedy, Paul A., Burlingame. Died Dec 1993, aged 81. Graduate of Jefferson Medical College, Philadelphia, Pennsylvania, 1939. Licensed in California in 1961. Dr Kennedy was a member of the San Mateo County Medical Association.

Koch, Eugene R., Newport Beach. Died Dec 22, 1993, aged 80. Graduate of University of Southern California, Los Angeles, 1941. Licensed in California in 1941. Dr Koch was a member of the Orange County Medical Association.

Miller, James S., Hemet. Died Jan 30, 1994, aged 58. Graduate of Stanford University School of Medicine, Stanford, California, 1959. Licensed in California in 1959. Dr Miller was a member of the Riverside County Medical Association.

Mullem, Maurice, Crescent City. Died Feb 6, 1994, aged 50. Graduate of Albert Einstein College of Medicine, Bronx, New York, 1967. Licensed in California in 1979. Dr Mullem was a member of the Humboldt-Del Norte Medical Society.

O'Hare, John F., San Jose. Died Jan 25, 1994, aged 81. Graduate of Northwestern University Medical School, Chicago, Illinois, 1940. Licensed in California in 1940. Dr O'Hare was a member of the Santa Clara County Medical Association.

Orlando, P. Johann, La Mesa. Died Feb 3, 1994, aged 73. Graduate of Medical College of Wisconsin, Milwaukee, 1944. Licensed in California in 1951. Dr Orlando was a member of the San Diego County Medical Society.

Paxman, Joseph H., Hayward. Died Jan 13, 1994, aged 66. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1953. Licensed in California in 1954. Dr Paxman was a member of the Alameda-Contra Costa Medical Association.

Sanborn, Alvin L., Fontana. Died Dec 24, 1993, aged 83. Graduate of University of Southern California, Los Angeles, 1939. Licensed in California in 1939. Dr Sanborn was a member of the San Bernardino County Medical Society.

Saunders, William M., San Diego. Died Jan 22, 1994, aged 50. Graduate of University of Alberta Faculty of Medicine, Edmonton, 1974. Licensed in California in 1976. Dr Saunders was a member of the San Diego County Medical Society.

Smith, Kenneth McLane, Santa Ana. Died Nov 11, 1993, aged 81. Graduate of Pritzker School of Medicine, University of Chicago, Chicago, Illinois, 1937. Licensed in California in 1947. Dr Smith was a member of the Orange County Medical Association.

Sugimura, Gregory Iwao, Ventura. Died Jan 9, 1994, aged 49. Graduate of University of California, San Francisco, 1969. Licensed in California in 1970. Dr Sugimura was a member of the Ventura County Medical Society.

Timberlake, Philip F., Costa Mesa. Died Dec 23, 1993, aged 73. Graduate of George Washington School of Medicine, Washington, DC, 1945. Licensed in California in 1947. Dr Timberlake was a member of the Orange County Medical Association.

Yant, James H., Sacramento. Died Jan 17, 1994, aged 86. Graduate of University of Michigan Medical School, Ann Arbor, 1931. Licensed in California in 1936. Dr Yant was a member of the Sacramento-El Dorado Medical Society.

New Mexico Medical Society

Jelso, Samuel J., Albuquerque. Died Jan 19, 1994, aged 86. Graduate of Loyola University Medical School, Maywood, Illinois, 1932. Licensed in New Mexico in 1937. Dr Jelso was a member of the Greater Albuquerque Medical Association.

Trinosky, Frank G., Albuquerque. Died Jan 3, 1994, aged 75. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1952. Licensed in New Mexico in 1961. Dr Trinosky was a member of the Greater Albuquerque Medical Association.

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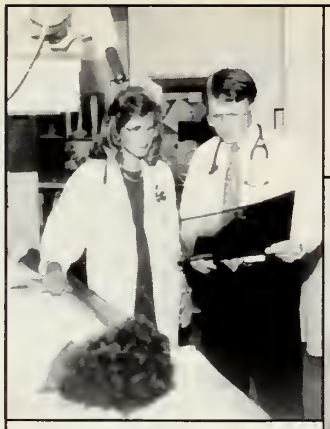

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PHYSICIANS. We are a six site Community Health Center located in central California. We have an opening at our clinic near Bakersfield for an Internist and a Family Practitioner. Competitive salary, revenue from hospitalization, excellent benefits, daytime hours, and limited call. Loan repayment available through NHSC. Contact George Laven, MD or George Johnston at (805) 845-3731.

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CODY, WYOMING has a year round position available for an Emergency Physician beginning September of 1994. Work in the beautiful Rocky Mountain region, located only 50 miles from Yellowstone Park. Area abundant in fishing, camping, boating, and all outdoor sports. NO STATE INCOME TAX!! For more information **call (307) 578-2488** or send CV to **Gary Bishop, Administrator, West Park Hospital, 707 Sheridan Ave, Cody, WY 82414.**

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HEAT WAVE? HAWAII, CALIFORNIA, UTAH, South Carolina, Florida, and Arizona clinics need Family Practitioners, Internists, Noninvasive Cardiologists and OBs. Hawaii—Hematologist/Oncologist, Gastroenterologist, $130,000. Benefits. Clear speech. CVs to LAM Associates, Dept W, 444 Hobron Ln, #207H, Honolulu, HI 96815-1229; Pat Lam, (800) 258-4526, (808) 947-9815, 11 am-8 pm PST.

CALIFORNIA. MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Medicine or Family Practice specialists preferred. Contact Rob Colyn, VP of Personnel, Doctors on Duty Medical Clinics, 19000 Portola Dr, Ste 100, Salinas, CA 93908; (408) 455-2424.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

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Our program offers a professionally stimulating environment, a quality lifestyle in the Pacific Northwest, signing bonus and a competitive salary/benefits package. Forward inquiry and C.V. to: W. J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., #300, Portland, OR 97210-5398. EOE.

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INTERNIST-PACIFIC NORTHWEST. The Everett Clinic, a 100 plus physician multispecialty group, is seeking BC/BE Primary Care Internist to associate with 12 person department. Clinic is 25 miles north of Seattle and has four rapidly expanding satellite offices. Everett has two accredited hospitals with 217 and 257 beds. Opportunity for exceptional personal/professional lifestyle. Position offers competitive salary with excellent benefits. Position open until filled. Send CV to Al Fisk, MD, The Everett Clinic, 3901 Hoyt Ave, Everett, WA 98201.

SALT LAKE CITY-URGENT CARE/FAMILY PRACTICE. Six-year-old center in upper middle class community. BC preferred, early partnership available. Great recreation area. Work Net, PO Box 26692, Salt Lake City, UT 84199.

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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: 1995, date and location to be announced.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 7-11, 1994, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 7-9, 1994, Ritz-Carlton Maunalani, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 28-30, 1994, Sun Valley.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1994, Holiday Inn, Great Falls.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1994, Coronado, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 5-7, 1994, Society Office, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-24, 1994, University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 22-24, 1994, Wenatchee.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 9-11, 1994, Jackson Lake Lodge, Moran.

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t1/2) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine. The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin. In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs. During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/− mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area ($mg/meter^2$). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General**.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhaboomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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AVAILABLE ON MEDI-CAL

Effective lipid management doesn't have to be tough

- Improves key lipids — significant reduction in LDL-C[1]
- Excellent safety profile
- Easy for patients — once-daily dosing, well tolerated
- Usual dose: 20 mg once daily at bedtime, with or without food

PRAVACHOL®

pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

Bristol-Myers Squibb Company

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Discover The Elegance Of A Hybrid

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At first glance, it's the enhanced performance of Vaseretic® that catches the eye. But study Vaseretic® more closely, and its *elegance* becomes apparent. The way its one-tablet, once-a-day dosage minimizes multiple medications. Minimizes the number of insurance copayments. And minimizes potassium supplementation.

A hybrid blending of tolerability and power that's available for the right patient. Vaseretic® is indicated for the treatment of hypertension in patients for whom combination therapy is appropriate.

And an elegant discovery for your practice.

VASERETIC® 10-25 *Next*

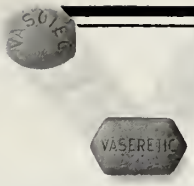
Enalapril Maleate-Hydrochlorothiazide

Vaseretic® is contraindicated in patients who are hypersensitive to any component of this product or to other sulfonamide–derived drugs and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.
Dosage must be individualized; the fixed combination is not for initial therapy.
Evaluation of the hypertensive patient should always include assessment of renal function.
For a Brief Summary of Prescribing Information, see adjacent pages.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

10 mg **25 mg**



USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General; Enalapril Maleate; Hypotension.* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions*, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy; Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*, below.)

Enalapril Maleate; Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats, and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide; Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General; Enalapril Maleate; Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions.*)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients; Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension. Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions; Enalapril Maleate; Hypotension—Patients on Diuretic Therapy. Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide; When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution

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assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse bone marrow assay.
Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.
Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.
Pregnancy: Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*
Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*
Clinical Laboratory Test Findings; Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.
Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide—Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

For more detailed information, consult your DuPont Pharma Representative or see Prescribing Information.

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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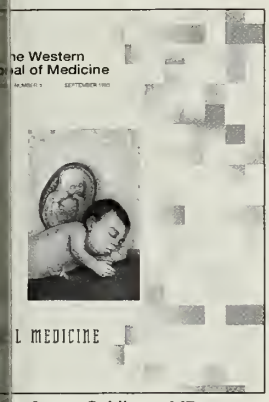

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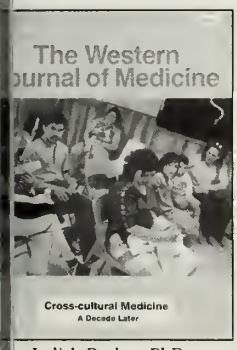

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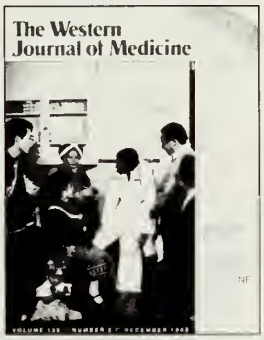

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CONTRAINDICATIONS

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Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive end have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravestatin end other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravestatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; treuma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy dunng treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosponne. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occesionally be associated with myopathy. The combined use of pravastatin and fibretes should generelly be avoided.**

PRECAUTIONS

Generel: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t1/2) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours affer cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time affer 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* [1 hour prior to PRAVACHOL (pravastatin sodium)], *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) affer 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated apropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs freated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) affer a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Hardenan gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimunum* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/− mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter^2). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General**.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitounnary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class.

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, penpheral neuropathy, penpheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interections.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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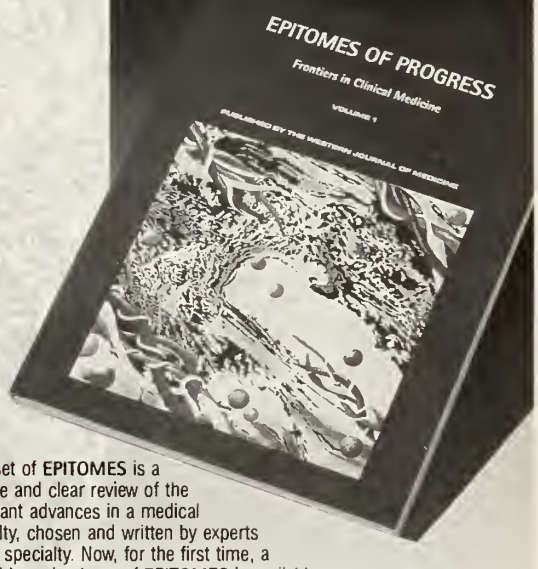

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

May 16-17—**Advanced Pediatric Life Support; Provider Course.** Maricopa Medical Center, Phoenix. Thurs-Fri. Contact: (602) 267-5414.

May 21—**Current Topics in Head and Neck Reconstruction.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Scottsdale. Sat. Contact: Tamara Zelinski, (602) 301-7447.

June 2-4—**Arizona Medical Association Annual Meeting.** Scottsdale Plaza Resort. Thurs-Sat. Contact: ArMA.

June 8-11—**Molecular, Immunologic, and Epidemiologic Approaches to Diagnosis of Systematic Mycosis and Drug Development.** University of Arizona College of Medicine at Northern Arizona University, Flagstaff. Wed-Sat. Contact: Lynn Mascarella, U of A.

June 9-10—**Advanced Cardiac Life Support: Provider Course.** Maricopa Medical Center, Phoenix. Thurs-Fri. Contact: (602) 267-5414.

October 28-30—**Arrthymias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Camelback Inn, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

November 7-11—**The Physician Management Seminar Series: Seminar I.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 7-11—**The Physician Management Seminar Series: Seminar II.** American College of Physician Executives at the Scottsdale Plaza Resort. Scottsdale. Mon-Fri. Contact: (800) 562-8088.

December 2-4—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Hyatt Regency, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

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ANESTHESIOLOGY

May 19-22—**California Society of Anesthesiologists Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $225-$325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

May 22-27—**Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun-Fri. 45 hrs. $500. Contact: UCSD.

CARDIOLOGY

June 3-5—**Pediatric Electrophysiology, Pacing Course, and Board Review.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. $425. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

July 22-24—**Coronary Heart Disease.** American College of Emergency Physicians at Marriott Tenaya, Yosemite. Fri-Sun. 11 hrs. Contact: Karen DeBont, Meetings Coordinator, 1500 W Canal Ct, Ste #500, Littleton, CO 80120-4528. (800) 421-3756.

July 24-28—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 19 hrs. Contact: UCD.

September 23-24—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Desert Inn, Las Vegas, NV. Fri-Sat. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

DERMATOLOGY

July 19-23—**11th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD and Scripps Clinic at La Jolla. Tues-Sat. 33 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037 (619) 554-8556.

August 8-10—**Dermatology for the Non-Dermatologists.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

June 17-20—**BLS Instructor Course.** CPR Seminars at San Leandro. Fri-Mon. $100. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

June 20-24—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 21-22—**5th Annual High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at Pan Pacific Hotel, San Francisco. Tues-Wed. 15 hrs. $450-$495. Contact: Alpen Travel and Meeting, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 451-RISK (7475).

July 19-20—**5th Annual High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at Pan Pacific Hotel, San Francisco. Tues-Wed. 15 hrs. $450-$495. Contact: Alpen Travel and Meeting, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 451-RISK (7475).

July 29—**ACLS Recertification.** CPR Seminars at San Francisco. Fri. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

August 15-19—**Emergency Medicine Symposium II.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

September 16—**Advanced Burn Life Support Course.** Torrance Memorial Burn Center at Torrance Memorial Hospital. Fri. 9 hrs. $220. Contact: Nancy Wise, (310) 517-4605.

September 17—**ACLS Recertification.** CPR Seminars at San Francisco. Fri. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

October 14-16—**Advances in Emergency Medicine.** Continuing Medical Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 17-21—**Emergency Medicine Symposium.** UCSD at San Diego Hilton. Mon-Fri. 17 hrs. $475. Contact: UCSD.

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Rancho Las Palmas Resort, Rancho Mirage, CA

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DEWEY K. ZIEGLER, MD
Dr Ziegler is Professor Emeritus, Department of Neurology, University of Kansas Medical Center, Kansas City.

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SUZANNE HAVALA, MS, RD, LDN
Ms Havala is Nutrition Advisor, The Vegetarian Resource Group, Charlotte, North Carolina.

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Dr Phillips is in private practice in Seattle, Washington.

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SOUTHERN ASSOCIATION FOR GERIATRIC MEDICINE, FOURTH ANNUAL MEETING
LOCATION: Hilton Head, South Carolina
SPECIALTY: Geriatrics
CME CREDIT: AMA Category 1
FEE: To be announced

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LOCATION: Williamsburg, VA
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FEE: TBA

JULY 18-21, 1994

FOCUS ON THE FEMALE PATIENT
LOCATION: Kiawah Island Resort, SC
SPECIALTY: OB/Gyn, Primary Care
CME CREDIT: AMA Category 1
FEE: SMA Members $350; Non-Members $475; Non-Physicians $225

JULY 22-24, 1994

FOCUS ON THE MALE PATIENT
LOCATION: Kiawah Island Resort, SC
SPECIALTY: Primary Care
CME CREDIT: AMA Category 1
FEE: SMA Member $310; Non-member $435; Non-Physician $225

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GENERAL SURGERY
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CENTER FOR ARTHRITIS AND JOINT IMPLANT SURGERY

The Center for Arthritis and Joint Implant Surgery at USC University Hospital is dedicated to bringing patients the combined proficiency of an experienced team, plus the distinct advantage of a university-based research program.

A Team Approach

Difficult and complex surgical procedures for the treatment of arthritis and joint replacements are offered at the Center. The staff has been working together as a team for 10 years and participates in:

- Surgical evaluation and planning
- Pre-operative patient education and medical evaluations
- Post-operative pain management and rehabilitation
- Extended care rehabilitation/management
- Close contact with referring physicians
- Grand rounds for physicians

Research Advantage

The Center conducts continuing research in the field of arthritis and joint implant surgery, specifically:

- Research into coatings along the surfaces of implants that increase the ability of the implant to stay bonded with bone.
- Research into articular surfaces that decrease wear and increase longevity of implants.
- Development of medicines that accelerate the healing process of bone around implants and secure prosthesis to bone.
- Ongoing design and development of new implant systems incorporating advances in metallic alloys and plastic technology.
- Development of surgical techniques that minimize muscular and ligament damage.

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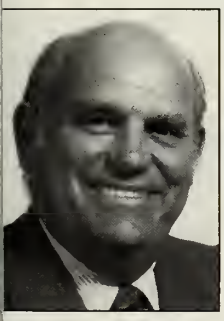

Lawrence D. Dorr, M.D., *director of the Center for Arthritis and Joint Implant Surgery at USC University Hospital, and professor of Orthopaedic Surgery at the University of Southern California School of Medicine, is a leader in joint replacement research, authoring more than 100 scientific articles. He has extensive surgical experience in joint replacement, which includes 2,500 hip and knee replacements in the past decade alone. He was named in the text of "Best Doctors in America" for 1992-1993.*

Dr. Dorr was the designer for the APR hip system, a pioneer in bone ingrowth fixation. He also designed the Apollo Hip and Knee Systems, which are modern cemented implants designed for economical longevity.

Edward J. McPherson, M.D., *assistant professor of Orthopaedic Surgery at the University of Southern California School of Medicine, is a member of the Center for Arthritis and Joint Implant Surgery at USC University Hospital. Dr. McPherson will head the revision service at the Center.*

Dr. McPherson's research interests include hip pain in athletes, the study of surface coatings to enhance bone ingrowth fixation in hip and knee replacements, and the study of articular surface coatings to reduce friction and wear. Additionally, Dr. McPherson has specialized interest and training in revision arthroplasty of the hip and knee, as well as experience with reconstruction and replacement of the shoulder and elbow.

Desmond M. Dall, M.D., F.R.C.S., *professor of Clinical Orthopaedics at the University of Southern California School of Medicine, is a member of the Center for Arthritis and Joint Implant Surgery at USC University Hospital.*

Dr. Dall has several major areas of research interest, including reconstructive surgery of the hip and knee, comparative functional evaluation of different antero-lateral approaches to the hip joint in total hip replacements, and the effect of muscular activity on the hip and endoprosthesis fixation. He also is investigating new fixation techniques in high tibial osteotomy and development of new techniques of internal fixation of long bones.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 414)

FAMILY PRACTICE/PRIMARY CARE

May 31-June 4—**21st Annual UCLA Family Practice Refresher Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Tues-Sat. 32 hrs. $485. Contact: UCLA.

June 4—**Asthma: A Challenge to Primary Care.** California Thoracic Society and American Lung Association at Laurel Heights Conference Center, San Francisco. Sat. 6 hrs. $85-$100. Contact: American Lung Association, (415) 543-4410.

June 12-17—**18th Annual Fingers to the Toes Orthopaedics for Primary Care.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. 25 hrs. Contact: UCD.

June 23-26—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 18 hrs. $370. Contact: UCLA.

July 5-7—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Tues-Thurs. 20 hrs. $350. Contact: UCSF.

August 5-7—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 19-21—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 19-21—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien, San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

June 4—**Heart Disease in the Elderly.** UCSF and Mount Zion Center on Aging at Miyako Hotel, San Francisco. Sat. Contact: Mount Zion Institute on Aging. (415) 750-4170.

October 7-8—**Coming of Age: Geriatrics for the Primary Care Provider—Part II.** UCD at Sacramento Inn. Fri-Sat. 13 hrs. $235. Contact: UCD.

1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

INFECTIOUS DISEASE

June 3—**8th Annual AIDS Conference.** Alta Bates Medical Center at Parc Oakland Hotel. Fri. 7 hrs. Contact: Caroline Carey, Medical Education, (510) 204-3884.

INTERNAL MEDICINE

May 20-22—**California Society of Internal Medicine Annual Meeting** at Hyatt Newporter Hotel, Newport Beach. Fri-Sun. 8 hrs. $100-$175. Contact: CSIM, PO Box 880606, San Francisco 94188-0606. (415) 882-5198.

May 23-27—**Advances in Internal Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 33 hrs. $630. Contact: UCSF.

June 4—**Pain Management.** Sutter Community Hospital at Jackson. Sat. Contact: Sutter Community, 2800 L St, Sacramento 95816. (800) 777-0231.

June 17-19—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. 12 hrs. Contact: Karen Debont, 1500 W Canal Crt, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 20-24—**Advances in Internal Medicine.** UCSF at Cole Hall, UCSF Campus. Mon-Fri. 33 hrs. Contact: UCSF.

July 9-16—**3rd National Kaiser Permanente Internal Medicine Conference.** Permanente Medical Group at Ritz-Carlton Hotel, Kapalua, Maui, Hawaii. 1 wk. 22 hrs. Contact: Eric Tepper, MD, 3400 Delta Fair Blvd, Antioch 94509. (510) 779-5211.

August 14-19—**11th Annual New Advances in Internal Medicine.** UCD at Hyatt Monterey. Sun-Fri. Contact: UCD.

August 26-September 1—**Comprehensive Nephrology Review Course.** UCLA School of Medicine at Beverly Hilton Hotel, Beverly Hills. Fri-Thurs. 51 hrs. $895. Contact: UCLA.

September 17-19—**1994 International Symposium on Bone Marrow Transplantation.** Sutter Community Hospital at Fairmont Hotel, San Francisco. Sat-Mon. Contact: Sutter Community, 2800 L St, Sacramento 95816. (800) 777-0231.

October 22—**Diabetes.** Sutter Community Hospitals at Sacramento. Sat. Contact: Peggy Coit, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

OB/GYN

October 1—**Colscopy.** Sutter Community Hospitals at Sacramento. Sat. Contacat: Lynne MacRae, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

October 8—**Women's Health.** Sutter Community Hospitals at Stockton. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

OCCUPATIONAL/ENVIRONMENTAL

June 3-4—**Occupational and Environmental Medicine.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

July 25-29—**8th Annual Sports Medicine.** UCSD at San Diego Princess Resort. Mon-Fri. 20 hrs. $395. Contact: UCSD.

ONCOLOGY

June 18—**Cancer.** Sutter Community Hospital at Sacramento. Sat. Contact: Sutter Community, 2800 L St, Sacramento 95816. (800) 777-0231.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 422)

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MAY 1994

1. Obstetrical Ultrasound
   May 12-15, 1994 Denver, CO
2. 22nd Annual Child Abuse and Neglect Symposium
   May 23-27, 1994 Keystone, CO

JUNE 1994

3. 40th Annual Family Practice Review
   June 12-18, 1994 Estes Park, CO
4. 7th World Conference on Lung Cancer
   June 26-July 1, 1994 Colorado Springs, CO

JULY 1994

5. Integrative Care of Head and Neck Cancer Patients
   July 1, 1994 Denver, CO
6. Treating the Hypoxic Patient
   July 5-9, 1994 Snowmass, CO
7. 30th Annual Internal Medicine Program
   July 10-15, 1994 Estes Park, CO
8. 21st Annual Renal Disease Program
   July 25-29, 1994 Aspen, CO
9. Cardiovascular Intervention: Technology at the Summit, IV
   July 21-August 3, 1994 Aspen, CO
10. 3rd Biannual Type I Diabetes Program
    July 31-August 3, 1994 Keystone, CO

AUGUST 1994

11. 18th Annual Dynamic Psychotherapy Program
    August 1-5, 1994 Aspen, CO
12. 37th Annual Pediatric Program
    August 7-11, 1994 Aspen, CO
13. 19th Annual Primary Musculoskeletal Care
    August 7-12, 1994 Breckenridge, CO
14. The Failing Pediatric Heart
    August 11-14, 1994 Aspen, CO
15. Breast Imaging and Intervention
    August 15-19, 1994 Colorado Springs, CO
16. 4th Annual Musculoskeletal Infection Course
    August 18-20, 1994 Snowmass, CO

SEPTEMBER 1994

17. The Changing Colors of Outreach Education
    September 16-18, 1994 Durango, CO
18. 3rd Annual Medical Ethics Conference
    September 16-18, 1994 Aspen, CO
19. Rocky Mountain Regional Cardiovascular Disease Conference
    September 30, 1994 Vail, CO

NOVEMBER 1994

20. 40th Annual Family Practice Review
    November 7-11, 1994 Denver, CO

(Continued from Page 420)

July 19-22—**Pan Pacific Lymphoma Conference.** University of Nebraska Medical Center at Ritz-Carlton-Mauna Lani, Kohala Coast, Hawaii. Tues-Fri. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

OPHTHALMOLOGY

May 20—**Annual Ophthalmology Alumni Symposium.** UCD at Vizcaya, Sacramento. Fri. 6 hrs. $85. Contact: UCD.

May 21—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

ORTHOPEDICS

May 19-21—**Fractures of the Shoulder and Elbow.** American Academy of Orthopaedic Surgeons at San Diego Marriott Hotel and Marina. Thurs-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

May 20-21—**New Techniques and Technologies in Total Hip Replacement.** American Academy of Orthopaedic Surgeons at Sheraton Palace Hotel, San Francisco. Fri-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

July 8-9—**Spine and Strength Symposium.** UCSD at Marriott, La Jolla. Fri-Sat. $300. Contact: Kerri Kazala, 4150 Regents Park Row #300, La Jolla 92037. (619) 625-0026.

July 15-16—**Hand Review 1994.** UCD at Holiday Inn, Capitol Plaza, Sacramento. Fri-Sat. $275. Contact: UCD.

July 23-30—**Update in Orthopaedics '94.** Kaiser Permanente Medical Center, South San Francisco at Hyatt Regency, Maui, Hawaii. Sat-Sat. 18 hrs. $425. Contact: Jerry VanMeter, MD, 1200 El Camino Real, So San Francisco 94080. (415) 742-2461.

August 13-17—**58th Annual Meeting Western Orthopedic Association at Long Beach.** Sat-Wed. 18 hrs. Contact: H. J. Martin, (510) 671-2164.

1994—**Educational Program for Musculoskeletal Evaluation and Rehabilitation.** UCSD at La Jolla. 35.5 hrs. $500. Contact: UCSD.

OTOLARYNGOLOGY

May 15-20 & June 5-10—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

PATHOLOGY

May 26-28—**10th Annual Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

August 13-20—**15th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton Mauni Lani, Big Island of Hawaii. Sat-Sat. 27 hrs. $950. Contact: UCSF.

September 17—**34th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott. Sat. Contact: National Kidney Foundation, 5777 W. Century Blvd, Ste 395, Los Angeles 90045-7404. (310) 641-8152.

September 17-21—**9th Combined Skin Pathology Course and 5th Annual Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sat-Wed. 40 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

June 1-3—**13th Annual Child Abuse and Neglect Conference.** UCD at Radisson Hotel, Sacramento. Wed-Fri. Contact: UCD.

June 3-5—**Pediatric Electrophysiology, Pacing Course and Board Review.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. $425. Contact: Children's Hospital, 30202 Children's Way, San Diego 92123. (619) 576-4072.

June 24-26—**Current Concepts in Child Neurology 1994.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15 hrs. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

July 15-17—**2nd Annual Pediatric Update.** Stanford University School of Medicine at Lucile Packard Children's Hospital, Palo Alto. Fri-Sun. Contact: Elinor Meyer, Medical Outreach Dept, 725 Welch Rd, Palo Alto 94304. (415) 497-8554.

August 22-24—**Pediatrics Update 1994.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 22—**Pediatrics.** Sutter Community Hospitals at Auburn. Sat. Contact: Lynne MacRae, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

PSYCHIATRY

June 28-July 3—**Neuropsychiatric Aspects of Aging: Update and Review.** Southern California Neuropsychiatric Institute at Mauna Kea Hotel, Hawaii. Tues-Sun. 22 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

October 7-11—**The Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Colonial Inn, La Jolla. Fri-Tues. 26 hrs. Contact: UCSD.

1994—**Basic Clinical Hypnosis Training.** UCSD at La Jolla. Ongoing. 30 hrs. $245. Contact: UCSD.

PULMONARY MEDICINE

June 5—**Pleuropulmonary Neoplasms.** California Tumor Tissue Registry at Westin South Coast Plaza, Costa Mesa. Sun. 8 hrs. Contact: Anne Chism, Loma Linda University, Department of Pathology, 11021 Campus Ave, AH 335, Loma Linda 92354. (909) 824-4788.

August 12-14—**Diagnosis and Management of Respiratory Diseases.** American College of Emergency Physicians at Hyatt Regency, Lake Tahoe, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

September 23-25—**Diagnosis and Management of Respiratory Diseases.** American College of Emergency Physicians at Esmeralda Resort, Palm Springs. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

RADIOLOGY

August 25-28—**Physics of Diagnostic Radiology.** UCD on Campus. Thurs-Sun. Contact: UCD.

October 10-14—**Neuroimaging Visiting Fellowship Program.** Stanford School of Medicine. Mon-Fri. 40 hrs. Contact: Barbara Platt, (415) 723-4733.

October 17-19—**Radiology for the Non-Radiologist.** UCSD at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $450. Contact: UCSD.

1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

1994—**Visiting Fellowship Program of Endovaginal Sonography: Focus on Techniques and Application.** UCSD Medical Center. Monthly. 30 hrs. $600. Contact: UCSD.

SURGERY

June 1-4—**Advanced Gynecologic Endoscopic Surgery.** Stanford Endoscopy Center. Wed-Sat. 25.75 hrs. Contact: Carl Levinson, MD, (415) 725-2551.

June 23-25—**20th Annual Meeting of the Western Thoracic Surgical Association.** WTSA at Resort at Squaw Creek, Olympic Valley. Thurs-Sat. Contact: WTSA, (508) 526-8330.

September 9-13—**Summer Institute—Intensive Surgical Skills.** American Academy of Orthopedic Surgeons at Monterey Conference Center, Marriott Hotel and Doubletree Hotel, Monterey. Fri-Tues. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

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(Continued from Page 422)

October 29—**Suture Workshop.** Sutter Community Hospitals at Sacramento. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

GENERAL/MULTIDISCIPLINARY

May 21—**Risk Management.** Sutter Community Hospital at Sacramento. Sat. Contact: Sutter Hospital, 2800 L St, Sacramento 95816. (800) 777-0231.

June 10-12—**7th Annual Medical Office Laboratory.** San Diego State University at Doubletree Hotel Horton Plaza, San Diego. Fri-Sun. 20 hrs. $425. Contact: Nancy Geiser, (619) 594-6255.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 12-18—**40th Annual Family Practice Review.** University of Colorado Health Sciences Center at YMCA of the Rockies, Estes Park. Sun-Sat. Contact: U of Colo.

July 8-10—**Common Problems in Primary Care.** P/SL Swedish Healthcare System at Snowmass. Fri-Sun. Contact: Nancy Manuel, (303) 788-6209.

July 8-10—**Current Concepts in Heart Failure: Medical Treatment to Mechanical Support and Transplantation.** P/SL Swedish Healthcare System at Snowmass. Fri-Sun. Contact: Nancy Manuel, (303) 788-6209 or P/SL CME Office, (800) 633-6824.

August 1-5—**Dynamic Psychotherapy Program.** University of Colorado Health Sciences Center at Aspen. Mon-Fri. Contact: U of Colo.

August 7-12—**19th Annual Primary Musculoskeletal Care Program.** University of Colorado Health Sciences Center at Breckenridge. Sun-Fri. Contact: U of Colo.

August 11-14—**Multimodality Approaches to Limb Salvage for Extremity Sarcoma.** P/SL Swedish Healthcare System at Westin Resort, Vail. Thurs-Sun. Contact: P/SL CME Office, (800) 633-6824.

August 14-17—**Fourth National Kaiser Permanente Emergency Medicine Conference.** Colorado Medical Society and Colorado Permanente Medical Group at Beavercreek. Contact: KPEM 94, PO Box 7131, Corte Madera, CA 94976-7131. (415) 927-7450.

August 15-20—**Breast Imaging and Intervention Into the 21st Century.** Radiology Imaging Associates at Broadmoor Hotel, Colorado Springs. Sun-Fri. Contact: Ryals & Associates, (404) 641-9773.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

Every Friday (except 4th Friday of month)—**Various Topics in Contemporary Medicine (Midday CME Series).** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

July 28-30—**Idaho Medical Association—Annual Meeting.** Sun Valley. Wed-Fri. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 14-17—**Sports Medicine and Imaging.** The Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 18-22—**Imaging 1994.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 7-11—**Lovelace Santa Fe Neurology 1994.** Eldorado Hotel, Santa Fe. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 16-17—**Annual Meeting—American College of Surgeons, New Mexico Chapter.** Hotel de Santa Fe, Santa Fe. Contact: Bonnie Smith, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237.

October 5-9—**3rd Annual New Mexico Medical Computer Course.** Holiday Inn Pyramid Hotel, Albuquerque. Contact: Floyd Smith, NMOMA, PO Box 90396, Albuquerque 87199-0396. (505) 828-1905.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

(Continued on Page 424)

CONTINUING MEDICAL EDUCATION

(Continued from Page 423)

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

May 18-20—**Odgen Surgical-Medical Annual Meeting.** Ogden Park Hotel, Ogden. Wed-Fri. 21 hrs. Contact: KayLynne, (801) 625-3122.

September 21-24—**Utah Medical Association—Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: Utah Medical Association.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

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DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 13-14—**WCAAP—Issues for Washington Children.** Seattle. Fri-Sat. Contact: Children's, (206) 526-2501.

May 20—**Clinical Guidelines.** Tacoma. Fri. Contact: PCMS CME.

May 20-21—**Orthopedic Pathology Review.** Seattle. Fri-Sat. Contact: Children's, (206) 526-2501.

June 5-8—**1994 Annual Meeting of the Society for Vascular Surgery and the North American Chapter, International Society for Cardiovascular Surgery.** Seattle. Sun-Wed. Contact: SVS/NA-ISCVS, (508) 526-8330.

June 13—**Diseases of the Nervous System—Update.** Seattle. Mon. Contact: U/W.

June 17—**Interventional Radiology.** Seattle. Fri. Contact: U/W.

June 18-19—**Pediatric Advanced Life Support.** Seattle. Sat-Sun. Contact: Children's, (206) 368-4802.

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July 29-30—**From Bench to Bedside: A State of the Art HIV Conference for Primary Care Providers.** Seattle. Fri-Sat. Contact: U/W.

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August 8-13—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Sat. Contact: U/W.

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September 10-11—**Pediatric Advanced Life Support.** Seattle. Sat-Sun. Contact: Children's, (206) 368-4802.

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September 29-30—**New Approaches to Common Urinary Tract Problems in Children.** Seattle. Thurs-Fri. Contact: Children's, (206) 526-2501.

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November 3-4—**Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 4—**Muscular Dystrophy and Related Disorders.** Seattle. Fri. Contact: Children's, (206) 526-2501.

November 11-12—**Pediatric Advanced Life Support.** Seattle. Fri-Sat. Contact: Children's, (206) 368-4802.

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COURSE SPONSORS AND CONTACT INFORMATION

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VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 9-11—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

Biomedical Science

Cytokines and Reproduction

CARLOS SIMÓN, MD, *and* MARY LAKE POLAN, MD, PhD, *Stanford, California*

Cytokines are important in reproduction. Interleukin-1, an established immune mediator, is one of the best-characterized members of the cytokine family. We describe what is known about the interactions between the interleukin-1 system and the hypothalamic-pituitary-gonadal, the hypothalamic pituitary-adrenal, and the hypothalamic-pituitary-thyroid axes. We also review the ovarian role of the interleukin-1 system. This cytokine has an immense and, as yet, imperfectly understood effect on the human reproductive tract. Clearly the immune system has a potential autocrine, paracrine, and endocrine role in regulating human reproductive events such as ovulation, luteinization, and implantation.

(Simón C, Polan ML: Cytokines and reproduction. West J Med 1994; 160:425-429)

For many years investigators and clinicians have attempted to understand the complexity of the human reproductive process. Anatomy, embryology, endocrinology, and other disciplines have been involved, but important questions remain unanswered. Recently a new immunologic approach to understanding the reproductive process appears to be illuminating.

Clinical and experimental evidence indicates that immune reactivity is greater in females than in males.[1] This condition provides females with an increased resistance to a variety of infections.[2] But women also have a much higher incidence of certain autoimmune diseases such as thyroid autoimmune diseases and systemic lupus erythematosus during the reproductive years.[3] These observations strongly suggest that the reproductive system plays an important role in the regulation of the immune system. Conversely, advances in the basic understanding of the immune system have provided new insights about the relevance of immune mediators in the reproductive system.[4] In particular, polypeptides produced by lymphocytes and monocytes, which were originally called lymphokines and monokines, respectively, are now known to be produced in various tissues other than leukocytes. They have also been found to have a broad spectrum of normal and disease-related actions on the reproductive system in addition to the regulation of immune functions.[5] The more generic term, cytokine, has replaced the terms lymphokine and monokine in common use.

The catalog of cytokines is still expanding. It includes interleukins 1 to 13 (IL-1 to -13), tumor necrosis factor α and β, transforming growth factor β, interferon α, β, and γ, leukocyte inhibitory factor, and colony-stimulating factor 1. All of these factors are polypeptides and act on a variety of target cells through specific plasma membrane receptor proteins[6] in a non-antigen-specific manner. A typical action is defined as autocrine or paracrine (feedback action on the cell that produces the cytokine or action on the surrounding cells), but not commonly considered endocrine. In this review, we present evidence of IL-1 endocrine actions.

Interleukin-1 System

The introduction of a foreign stimulus elicits a complex response that must have evolved to protect persons from the invasion of substances from outside the self.[7] Interleukin-1 is one of the earliest, if not the first, cytokine produced by macrophages or monocytes in response to these stimuli and is essential for the immune cascade. Interleukin-1 is not produced exclusively by cells of the immune system; rather, it is also a product of many cell types, such as fibroblasts and epithelial cells. Furthermore, its effects are not restricted to leukocytes but are manifested in other cells of various tissues modulating immune, neuroendocrine, and metabolic functions.[8]

Interleukin-1 is a family composed of three structurally related polypeptides. Two are agonists: interleukin-1α (IL-1α) and interleukin-1β (IL-1β), and one is an inhibitor, interleukin-1 receptor antagonist (Figure 1). Although the genes for IL-1α and IL-1β are different and located on separate areas of chromosome 2, both recognize the same receptor on target cells and produce similar biologic effects.[9] Molecular cloning of IL-1α and IL-1β genes has revealed a nucleic acid homology of 45% and a surprisingly low amino acid homology of only 26%; in addition, both molecules have distinct isoelectric points (pI 5 and 7, respectively). The primary amino acid sequence of mature IL-1β is conserved among the various animal species in the range of 75% to 78%, whereas the α-sequence is conserved in the range of 60% to 70%.[8] In addition, IL-1α and IL-1β genes are differentially expressed in various tissues.[10] The two forms of IL-1 are initially synthesized as intracytoplasmic 31-kd precursors.

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ABBREVIATIONS USED IN TEXT

CRH = corticotropin-releasing hormone
FSH = follicle-stimulating hormone
HPA = hypothalamic-pituitary-adrenal
IL-1 = interleukin-1
LH = luteinizing hormone
mRNA = messenger RNA
TSH = thyroid-stimulating hormone

The precursor to IL-1 is cleaved by IL-1β converting enzyme,[11] generating a carboxyl-terminal 17-kd peptide called "mature" IL-1β that is the biologically active form and is released by the cell to the extracellular space and the circulation. The IL-1α precursor is transported to the cell surface and anchored to the plasma membrane. Unlike the IL-1β precursor, the IL-1α precursor is biologically active. Finally, IL-1 precursors are cleaved to yield mature molecules of 159 amino acids (IL-1α) and 153 amino acids (IL-1β) when released from the cells.

The IL-1 receptor antagonist is another polypeptide that competes with IL-1α and -β for IL-1 surface receptor occupancy.[12] It is a specific inhibitor of interleukin-1 activity that acts by blocking the binding of IL-1 to its cell surface receptors.[13] This remarkable difference is important for cytokine biology. The complementary DNA for the IL-1 receptor antagonist encodes a 152-amino acid protein, which shows a striking similarity with IL-1α and IL-1β molecules. This molecule provides some protection against the manifestations of disease provoked by IL-1. Further evidence of relevancy is provided by studies that have shown that IL-1 receptor antagonist is synthesized in animals with sepsis and reduces the severity of septic shock and colitis induced by IL-1.[14,15] Preliminary clinical studies suggest that IL-1 receptor antagonist may be beneficial in patients with sepsis.[16]

There are two IL-1 receptors, now indicated as IL-1 receptor type I and type II, and corresponding to the 80-kd and 68-kd IL-1 binding proteins on the plasma membranes of T and B cells, respectively.[17,18] Both are members of the immunoglobulin superfamily, and they are structurally related to each other. The type I receptor is found primarily on T cells, whereas the type II receptor is found on neutrophils, B cells, and bone marrow cells. Some cells, however, such as monocytes, probably express both types, and both may cooperate in binding and signal transduction. Interleukin-1α has a higher affinity for the type I receptor, whereas IL-1β has a greater affinity for the type II receptor. Nonetheless, both receptors recognize the α and β forms of IL-1. The receptor antagonist of IL-1 recognizes the type I receptor, but information regarding its affinity for the type II receptor is unclear. Also, a natural soluble form of IL-1 receptor has been identified in body fluids.[19] This soluble receptor is generated by proteolytic cleavage of the extracellular portion of the type II receptor. A general feature of receptor-ligand interactions is the internalization of the complex by receptor-mediated endocytosis.[20] Presumably when the two IL-1 receptor types are present in the same cell, they function independently at the level of ligand binding and do not form a heterodimeric receptor complex.[21] There is still no clear consensus regarding the role of classical second messengers in IL-1 action; what appears certain is that in EL4 cells, IL-1β signals through the sphingomyelin pathway.[22]

Interactions Between the Interleukin-1 System and the Hypothalamic-Pituitary-Gonadal Axis

Infection and inflammation are usually accompanied by a central inhibition of reproductive function, as in patients with sepsis and burns, for example. Interleukin-1 has been reported to be produced by central neurons, glial cells, and brain macrophages.[23-25] It has also been shown that the hypothalamus and hippocampal neurons contain a high density of IL-1 receptor type I.[26] To elucidate the mechanism whereby IL-1 may be involved in the regulation of the hypothalamic-pituitary-gonadal axis, several authors have studied the effect of IL-1α and IL-1β on the rat hypothalamic-pituitary-gonadal axis in vivo and in vitro (Figure 2).[27-29] Their results suggest that the intracerebroventricular administration of IL-1 acts at the central level by inhibiting the release of both gonadotropin-releasing hormone and luteinizing hormone (LH), with a specificity sufficient to exclude an effect on the secretion of follicle-stimulating hormone (FSH).[30] In normal human subjects, plasma concentrations of IL-1β are usually below the level of detection, except in women after ovulation[31] or in subjects after strenuous exercise. In patients with burns and sepsis, increased plasma levels of IL-1β are frequently associated with reduced LH and testosterone levels.[32,33] Also, the capability of IL-1 to increase the pituitary secretion of prolactin and growth hormone in patients with acute immune reactions has been demonstrated.[34] Prolactin is required for the normal maintenance of lymphoid tissues and immune responses of macrophages and T and B cells in rodents.[35] The inhibition of the pituitary release of prolactin by bromocriptine administration in rats selectively reduces lymphocyte reactivity in vitro and in vivo, whereas the immune deficiency of hypophysectomized rats is reversed by pro-

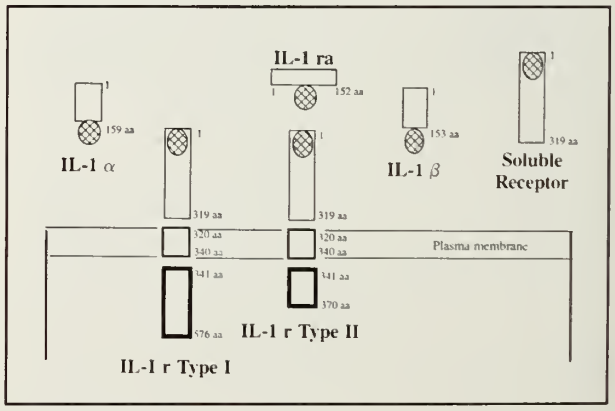

Figure 1.—The diagram shows the interleukin-1 (IL-1) family. Circles represent the receptor site that is shared by all the members of the family. aa = amino acid numbers; IL-1 ra = interleukin-1 receptor antagonist; IL-1 r type I, type II = interleukin-1 receptor type I, type II

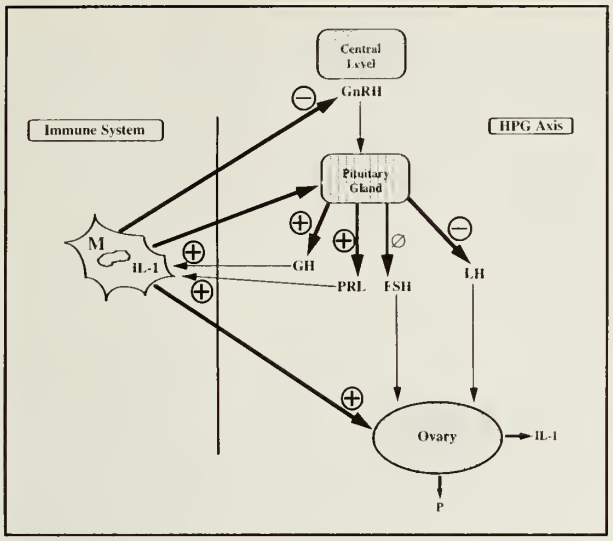

Figure 2.—The diagram represents the interactions between interleukin-1 (IL-1) and the hypothalamic-pituitary-gonadal (HPG) axis. FSH = follicle-stimulating hormone, GH = growth hormone, GnRH = gonadotropin-releasing hormone, LH = luteinizing hormone, M = macrophages, P = progesterone, PRL = prolactin, ➡ = effects produced by IL-1 on hormonal regulation, → = effects produced by hormones on IL-1 regulation, + = stimulatory effect, − = inhibitory effect, ∅ = no effect

lactin, placental lactogen, or growth hormone, but not other pituitary hormones.[36]

The IL-1 system also acts at the level of the gonads. Previous studies have established in pigs,[37,38] mice,[39,40] hamsters,[41] and humans[42] that the ovaries are the site for IL-1 reception and action. In these animal models, IL-1 imparts potent antigonadotropic[37-40] or steroidogenic[41] effects under various experimental conditions. In humans, this steroidogenic effect is controversial. Both human peripheral blood monocytes and peritoneal macrophages have been shown to be capable of stimulating progesterone production by granulosa-lutein cells.[43] Although IL-1β is the likely candidate for this stimulatory effect, the action of IL-1β or IL-1α on either basal or human chorionic gonadotropin-stimulated estradiol or progesterone production by cultured human granulosa-lutein cells remains controversial and may depend on specific culture conditions and IL-1 preparations. Also relevant to granulosa cell differentiation is the finding that the number of LH receptors induced by FSH is inhibited by IL-1 in rat granulosa cells,[39,40] and this inhibition of LH receptor development by IL-1β is dose-dependent and time-related.[40]

Not only does IL-1 modulate steroid and gonadotropin secretion, but gonadotropins and gonadal steroids, in turn, have been shown to interact with the immune system and modulate the secretion of IL-1. There are several explanations for this surprising hormonal regulation of the immune response:

- Human lymphocytes secrete immunoreactive and bioactive LH, FSH, or human chorionic gonadotropin.[44,45]
- The presence of LH-releasing hormone receptors on porcine lymphocytes has been demonstrated,[46] suggesting that gonadotropin production by lymphocytes may be triggered by gonadotropin-releasing hormone.
- Gonadotropins regulate IL-1 messenger RNA (mRNA) expression in various cell types other than hematopoietic cells. In fact, the gonadotropin-dependent preovulatory induction of IL-1 transcripts in the theca-interstitial cell layer in murine[47] and human[42] ovaries specifically implicates the IL-1 system in the preovulatory cascade. Furthermore, an ovulatory effect of IL-1 has been documented in vitro in perfused rat ovaries[48] and in perfused rabbit ovaries.[49] These results suggest an autocrine-paracrine action of IL-1 in the ovary, especially during ovulation.
- Human monocyte production of IL-1β is regulated by gonadal steroids. We have shown that cultured peripheral monocytes isolated during the late luteal phase secrete substantially higher levels of IL-1β than cultured monocytes isolated during the preovulatory follicular phase.[50] In addition, low levels (10^{-9} mol per liter) of the gonadal steroids, estradiol (E_2) and progesterone, may stimulate, and at higher levels ($\geq 10^{-7}$ mol per liter) substantially inhibit, IL-1 activity[51] and IL-1β mRNA levels[52] of both peripheral monocytes and placental macrophages. Also, estradiol modulates IL-1 production by macrophages.[53] This correlation is supported by the reduced synthesis of IL-1 by macrophages in rats whose ovaries were removed and an increment in IL-1 synthesis after estradiol replacement in vivo and in vitro.[53] These results together suggest a hormonal regulation of IL-1 production. This remarkable endocrine feedback regulation between IL-1 and ovarian steroids may be another regulatory loop important for the ovulation or luteinization processes.

Multiple autocrine-paracrine-endocrine loops exist between the immune and reproductive systems, further suggesting a remarkable feedback regulation between them that controls ovulation, luteinization, or both.

Interactions Between the Interleukin-1 System and the Hypothalamic-Pituitary-Adrenal Axis

Hormones produced by the adrenal gland have important effects on the reproductive system. Hyperfunction and hypofunction of the adrenal gland result in chronic anovulation and amenorrhea.

The IL-1 system activates the hypothalamic-pituitary-adrenal (HPA) axis at different levels (Figure 3). Intravenous or intracerebroventricular administration of IL-1 produces a prompt rise in corticotropin-releasing hormone (CRH) release at the hypothalamic level, leading to increased plasma levels of adrenocorticotropin, or corticotropin, within 30 minutes after administration. Direct effects on the pituitary corticotrophs are not as clear; however, a stimulatory effect by IL-1 on corticotropin secretion from human pituitary adenoma cells has been reported. Corticotropin-releasing hormone receptors exist in peripheral sites of the immune system, and CRH directly stimulates leukocytes to produce IL-1. Finally, cytokines including IL-1 also act directly on the adrenal cortex to enhance prostaglandin E_2 production and corticosterone re-

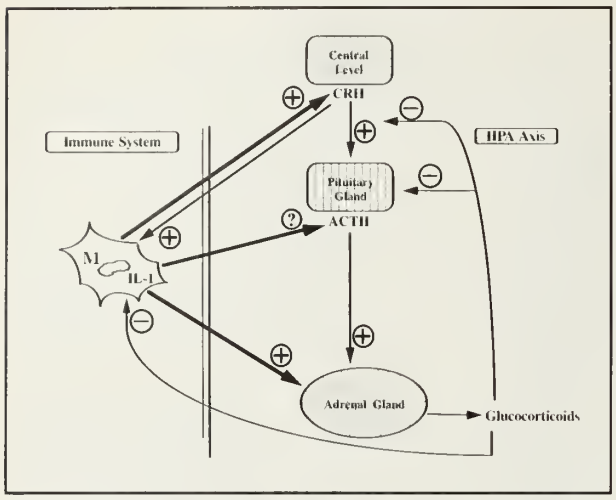

Figure 3.—The diagram represents the interaction between interleukin-1 (IL-1) and the hypothalamic-pituitary-adrenal (HPA) axis. ACTH = adrenocorticotropin hormone (corticotropin), CRH = corticotropin-releasing hormone, M = macrophages, ➡ = effects produced by IL-1 on hormonal regulation, → = effects produced by hormones on IL-1 regulation, + = stimulatory effect, − = inhibitory effect, ? = unknown

lease. The end point of all of these mechanisms is the IL-1-mediated increase of glucocorticoids by the HPA axis.[54]

There is evidence that glucocorticoids participate in a feedback loop with the IL-1 system and the HPA axis itself and exert an adverse effect on the immune system. Glucocorticoids inhibit IL-1-induced CRH release[55] and corticotropin production at the pituitary level.[54] Also, glucocorticoids inhibit the production or secretion of IL-1 in peritoneal macrophages[56] and specifically in cells present at the locus of inflammation. Therefore, it seems that IL-1 activates the HPA axis to elevate circulating glucocorticoid levels when an immunogenic challenge is presented, and glucocorticoids, in turn, inhibit excessive activation of the HPA axis and modulate many immune activities including IL-1 secretion. Also, glucocorticoids have inhibitory effects on inflammatory loci to reduce locally the production or secretion of cytokines. Once activated, cytokines could be highly toxic if they are not properly modulated. Such a regulatory circuit might explain the abnormal process of some diseases with an immune pathogenesis such as human cyclic neutropenia, Hashimoto's thyroiditis, and Lyme disease.[55]

Interactions Between the Interleukin-1 System and the Hypothalamic-Pituitary-Thyroid Axis

Thyroid disease not only occurs more commonly in women but also interferes with the reproductive function. It is well known that serum thyroid hormone levels change in severe illness, and thyroid dysfunction has been linked to reproductive failure through either anovulation or pregnancy wastage. Such abnormality is called "euthyroid sick syndrome" and is thought to be mediated, at least in part, by the effects of cytokines on the hypothalamic-pituitary-thyroid axis. The subcutaneous administration of IL-1β decreases plasma thyroid hormone and thyroid-stimulating hormone (TSH) levels in rats.[57] The inhibitory effect is not only at the pituitary level but also on the thyroid independent of TSH levels.[58] Direct action of IL-1 on thyroid cells has been shown with in vitro experiments. A small amount of IL-1 enhances thyroglobulin mRNA transcription, thyroglobulin secretion, and iodide organification induced by TSH, but larger doses suppress them.[59] Finally, the observation that IL-1 enhances the biosynthesis of somatostatin, a TSH release-inhibiting factor, in cultured hypothalamic neurons[60] suggests again that the hypothalamus is one of the sites of IL-1 action.

In summary, IL-1 inhibits the hypothalamic-pituitary-thyroid axis, acting at different levels. This cytokine acts at the level of the hypothalamus and pituitary to inhibit TSH secretion. Also, IL-1 inhibits the biosynthesis and release of thyroid hormone and thyroid cell growth, especially at large doses. The direct inhibitory action of this cytokine on the hypothalamus-pituitary-thyroid axis and the influence of the axis in reproduction may help to explain the pathogenesis of autoimmune hypothyroid disorders and their deleterious effects on reproduction.

Conclusion

Over the past decade, cytokines have become of increasing interest to reproductive scientists and clinicians. The function and actions of IL-1 are perhaps the best documented of all the cytokines in the area of reproduction. In this monograph, we have reviewed evidence of the relationship between the immune system and the reproductive endocrine system and the role of IL-1 in this interaction. It is well known that normal reproductive function relies on correct function and interaction among the hypothalamic-pituitary-gonadal, the hypothalamic-pituitary-adrenal, and the hypothalamic-pituitary-thyroid axes. Hence, we have reviewed the interactions between the IL-1 system and these three axes as well as the role of the IL-1 system in the ovary. Little is known of the presence and regulation of IL-1 receptors, and less is known about the interaction of IL-1 and its receptor with IL-1 receptor antagonist in the female reproductive system. Also, the actions of this cytokine may be different in different cell types (pleiotropy) or within different endocrine environments. More time and effort are required to learn about the interactions between the cytokine IL-1 and the reproductive system to fully understand processes such as ovulation and luteinization. Another area where IL-1 appears to be relevant in human reproduction, but was not reviewed here, is at the level of trophoblast-endometrial interaction. This field, which has recently emerged, has profound implications in fetal immune recognition leading to successful implantation and promises to generate exciting new concepts in reproductive immunology.

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Articles

Moose Soup Shigellosis in Alaska

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Following a community gathering held in early September 1991, an outbreak of gastroenteritis occurred in Galena, Alaska. We conducted an epidemiologic investigation to determine the cause of the outbreak. A case of gastroenteritis was defined as diarrhea or at least 2 other symptoms of gastrointestinal illness occurring in a Galena resident within a week of the gathering. Control subjects included asymptomatic residents who either resided with an affected person or were contacted by us during a telephone survey. Of 25 case-patients, 23 had attended the gathering compared with 33 of 58 controls. Among persons who attended the gathering and from whom we obtained a food consumption history, 17 of 19 case-patients and 11 of 22 controls ate moose soup. No other foods served at the gathering were associated with illness. Ten case-patients had culture-confirmed *Shigella sonnei*. Many pots of moose soup were served each day, and persons attended the gathering and ate moose soup on more than 1 day. Moose soup was prepared in private homes, allowed to cool, and usually served the same day. We identified 5 women who had prepared soup for the gathering and in whose homes at least 1 person had a gastrointestinal illness occur at the time of or shortly before soup preparation. This investigation suggests that eating contaminated moose soup at a community gathering led to an outbreak of shigellosis and highlights the risk of eating improperly prepared or stored foods at public gatherings.

(Gessner BD, Beller M: Moose soup shigellosis in Alaska. West J Med 1994; 160:430-433)

On September 11, 1991, a nurse practitioner at the clinic in Galena, Alaska, notified the Alaska Division of Public Health of an outbreak of illness characterized by fever, chills, muscle aches, and diarrhea among persons who had recently attended a community gathering called a potlatch. The next day, a person who had attended the potlatch and who was subsequently admitted to a hospital was diagnosed with laboratory-confirmed shigellosis. We initiated an investigation to characterize the outbreak and determine possible causes.

Galena is a predominantly Alaska Native village located in the central part of the state; the provisional population estimate as of July 1, 1991, was 829. A potlatch is a traditional Alaska Native community gathering held over one or more evenings. Many persons may bring similar foods to a potlatch, and each person attending may bring more than one type of food. Galena residents estimated that 300 to 500 persons of all ages attended each day of a potlatch held in the high school gymnasium on September 5 to 7 and 9. The facility was equipped with running water and flush toilets.

Patients and Methods

We defined a case of gastroenteritis as an illness in a person from Galena, with onset from September 6 to 13, consisting of diarrhea (≥3 watery stools in a 24-hour period) or at least two of the following symptoms: fever or chills, nausea or vomiting, abdominal pain, bloody stools, or mucus in the stools. During the initial case finding, we obtained a list of persons with acute gastrointestinal symptoms who had visited the Galena clinic—the only health facility in the village—from September 6 to 13. We went to the clinic on September 13 and 14, contacted persons on the list, and administered a standardized questionnaire to them and their household members. The questionnaire solicited information on demographic data, illness characteristics, dates of potlatch attendance, specific foods eaten at the potlatch, and food brought to the potlatch.

We expanded our case finding from September 13 to 20 by calling all 116 residential numbers listed in the Galena telephone directory a maximum of three times and administering the questionnaire to residents of each of the 19 households where at least one adult was located. Most unsuccessful attempts resulted from disconnected telephone numbers; no persons contacted refused to participate. Because of increasing difficulty with recall, after September 15 we did not ask residents which foods they had eaten at the potlatch.

Because we determined that potlatch attendance was a risk factor for illness, we further evaluated the risk among persons who had attended the potlatch. For this

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ABBREVIATIONS USED IN TEXT

CI = confidence interval
OR = odds ratio

analysis, case-patients were restricted to persons with illness occurring within 12 to 96 hours—the usual incubation period for shigellosis—after attendance at the potlatch. For control subjects, we selected non-ill interviewees who had attended at least one day of the potlatch.

Because acquired immunity might have prevented illness even if a substantial exposure occurred during the potlatch, persons who had illness consistent with the case definition but with onset between August 7 and September 5 (the first day of the potlatch) were not included as either cases or controls. Because many persons had difficulty recalling the exact foods they consumed at the potlatch, we analyzed food consumption using the following categories: salad (leaf, fruit, pasta, potato), moose soup (a homemade soup containing moose meat), local meat (moose, duck, bear), store-bought meat (turkey, ham), fish, Indian ice cream (lard from various animals mixed with sugar and wild berries), frybread, and dessert.

All ill residents whom we interviewed on September 13 or 14 were requested to submit a stool specimen. Fresh stool was collected by the patient or a parent or guardian and placed in Carey-Blair transport media. Cultures were performed by the State Public Health Laboratory, Anchorage.

Odds ratios (OR) and Cornfield confidence intervals (CI) were determined using Epi Info computer software.[1] When an expected cell size was 5 or less, we used exact confidence intervals.

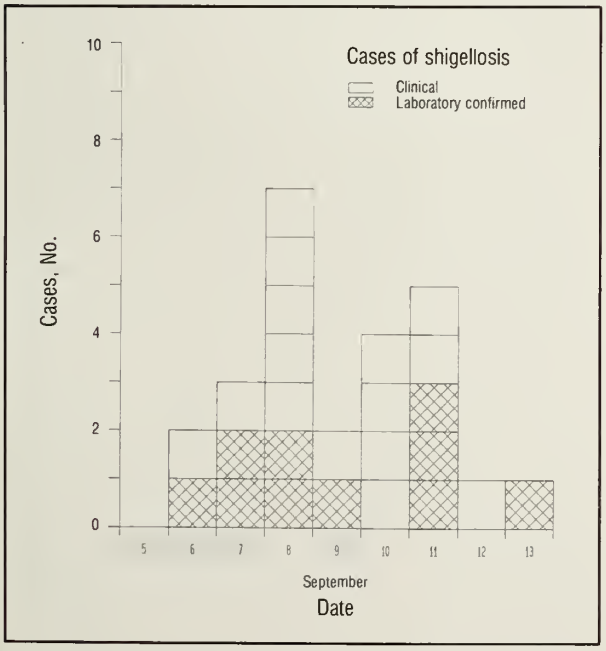

Figure 1.—Cases of shigellosis are depicted by day of onset for the outbreak in Galena, Alaska, from September 6 to 13, 1991. Shaded days indicate dates of the potlatch.

TABLE 1.—*Case-Patients and Controls Who Consumed Particular Foods at a Potlatch, Galena, Alaska, 1991*

Food	Case-Patients (n = 19), No.	Controls (n = 23), No.	Odds Ratio (95% CI)
Moose soup*	17	11	8.5 (1.4, 88.6)
Dessert	15	14	2.4 (0.5, 13.0)
Salad	14	14	1.8 (0.4, 8.6)
Meat, local	8	7	1.7 (0.4, 7.3)
Meat, store bought*	10	10	1.3 (0.3, 5.6)
Fish	5	5	1.3 (0.2, 6.8)
Frybread	4	4	1.3 (0.2, 8.0)
Indian ice cream	8	11	0.8 (0.2, 3.3)

CI = confidence interval

*Moose soup and meat (store bought) consumption history could not be recalled by 1 control each.

Results

A total of 100 persons were interviewed; 51 and 49 through the clinic and telephone survey, respectively. Of these, 17 had symptoms consistent with the case definition, but their illness had occurred from August 7 to September 5, so they were not included in further analysis. The illness onset dates for these 17 people were evenly distributed over the 29 days before the potlatch. Of the remaining 83 persons, 42 (51%) were female, and ages ranged from 6 months to 76 years (median, 26 years). Nearly a third (25) met the case definition; 12 were still sick when interviewed. Symptoms included diarrhea (21 [84%]), fever (20 [80%]), abdominal pain (20), chills (18 [72%]), nausea (17 [68%]), vomiting (11 [44%]), mucus in the stools (5 [20%]), and bloody stools (5). Illness incidence was bimodal with peaks on September 8 and 11 (Figure 1). Among those who had recovered and recalled the date their illness began, the median duration of illness was three days (range, 1 to 7 days). Of the 25 case-patients, 23 had attended the potlatch, compared with 33 of the 58 people who did not have illness meeting the case-definition (OR = 8.7; 95% CI = 1.8, 81.4).

Among the 56 persons who attended at least one day of the potlatch, attendance varied from 17 (30%) to 46 (82%) per day; 36 (64%) attended on two or more days. We selected the 56 persons who attended the potlatch for further study. Among persons asked about food consumption who were able to recall, 17 of 19 case-patients and 11 of 22 controls recalled eating moose soup (OR = 8.5; 95% CI = 1.4, 88.6). No other foods were implicated (Table 1). No persons ate only moose soup. Compared with controls, case-patients were nearly 4 times more likely to report eating moose soup on one day and 30 times more likely to report eating moose soup on two or more days (Table 2). Because most persons who attended the potlatch did so on at least two days and many had difficulty recalling the specific days they attended, we could not evaluate the risk of attending the potlatch on any particular day.

Environmental Investigation

We estimated that 10 to 15 pots of moose soup were

TABLE 2.—*Case-Patients and Controls Who Consumed Moose Soup on 0, 1, and ≥2 Days of a Potlatch, Galena, Alaska, 1991*

Days Moose Soup Consumed, No.	Case-Patients (n = 19), No.	Controls (n = 22), No.	Odds Ratio (95% CI)
0	2	11	Referent
1	6	9	3.7 (0.5, 43.8)
≥ 2	11	2	30.3 (2.7, 417.7)

CI = confidence interval

served each day of the potlatch. One or two pots were 15 liters; the rest were smaller. Soup was prepared by boiling moose meat for several hours in water and spices, sometimes with rice and vegetables added depending on the preference of the preparer. After cooking, soups were cooled for an estimated one to more than five hours and then served without reheating. Of four moose soup preparers interviewed, one said that some people brought soup to the potlatch that had been prepared for an earlier day of the potlatch.

The number of people who prepared moose soup each day was unknown. Five women were identified who had prepared moose soup for the potlatch and in whose homes at least one person had symptoms occur that met the case definition either at the time of or shortly before they prepared soup. Of these women, two were ill themselves, and one of these was still ill when she made moose soup. Two of the five preparers identified could not recall the specific days they brought moose soup to the potlatch; among the other three women, two each day brought soup on September 5, 6, and 7.

Laboratory Analysis

Of the 23 case-patients interviewed at the clinic on September 13 or 14, 13 submitted stool specimens for culture; 10 of these were positive for *Shigella sonnei*. All persons with a positive culture had their illness begin 12 to 96 hours after attending the potlatch.

Discussion

We describe an outbreak of shigellosis due to *S sonnei* that occurred in rural Alaska. In general, *S sonnei* is the most common *Shigella* serotype isolated in the United States and other developed countries.[2] In contrast, *Shigella dysenteriae* type 1, which produces Shiga toxin and a more virulent illness, occurs more frequently in developing countries.[3] Our investigation suggests that disease transmission was probably occurring for at least a month before the outbreak and that the ongoing transmission of *Shigella* species may have provided an opportunity for the outbreak to occur. The case-control study revealed an association between eating moose soup and illness. Illness in the homes of one or more food preparers concurrent with or shortly before moose soup preparation might have resulted in the contamination of soup with *S sonnei*. Alternatively, soup could have been inoculated at the potlatch by one of the people serving it. Because soup was allowed to cool before it was served and because leftover soup may have been served, bacterial growth may have occurred. The preparation of moose soup in one or two 15-liter pots suggests a possible mechanism for the spread of *S sonnei* to a large group of people who ate soup.

Because most people attended the potlatch on at least two days but many had difficulty recalling the specific days, we could not evaluate the risk associated with attendance or the consumption of moose soup on a particular day. It is possible that contaminated soup was served on more than one day, either from the same preparer or from two different preparers. The bimodal epidemic curve (Figure 1), together with the absence of a potlatch on September 8, suggests that contaminated soup may have been served first during September 5 to 7 and then again on September 9. The finding that the risk of illness was greater among persons who ate moose soup on multiple days is also consistent with the hypothesis that contaminated soup was served on more than one day. The latter finding could also be explained by an increased likelihood among persons who attended the potlatch on more than one day of being present on the single day that contaminated soup was served.

There are several limitations to the interpretation of these results. Five of the eight foods were eaten by a minority of persons who attended the potlatch. This may be because eating food at a potlatch is more important as a symbol of community participation than as a meal, and eating even small amounts of food may suffice for this purpose. Recall bias of either food consumption or date(s) of attendance could have resulted in the misclassification and underestimation or overestimation of effect. Collapsing foods into larger groups may have caused us to miss an association between a particular food and illness. Our data were also somewhat limited because we did not obtain food histories from people interviewed after September 15.

Shigellosis most commonly spreads as a result of person-to-person contact, although foodborne transmission has also been reported.[3-7] At a temperature of 25°C to 37°C, *Shigella* species has been shown to multiply exponentially in a variety of foods, including soup.[8] Mass gatherings represent an efficient mechanism for the widespread transmission of enteric pathogens; a major event in 1987 resulted in the nationwide dissemination of a multiple-antibiotic-resistant strain of *S sonnei* in the United States.[9] Because soup is usually served hot, it is an unusual vehicle.[4,7] Our investigation suggests that during multiday events, when leftovers might be served and when several hours elapse between preparation and consumption, soup should be considered a possible vehicle.

From 1968 to 1992, the Alaska Division of Public Health investigated four other shigellosis outbreaks with more than 10 cases (540 total cases); all but one outbreak occurred in rural areas (unpublished records). Rural Alaskans, such as those described in this report, may be at an increased risk of shigellosis because of geographic and cultural factors: the availability of running water may be limited; houses may be crowded with people indoors for

long periods, especially during the winter; and access to medical facilities for early diagnosis and treatment may be limited. In addition, community gatherings are common in rural Alaska; as we have reported in this investigation, endemic shigellosis can provide a setting in which common-source outbreaks occur.

To prevent secondary illness from this outbreak, we attempted to decrease *Shigella* species transmission by instituting appropriate control measures.[2,10,11] First, we conducted active surveillance for shigellosis by routinely contacting village health providers. We recommended that all persons with acute gastroenteritis have a stool culture and be treated with the combination of trimethoprim and sulfamethoxazole.[12] Second, we recommended that antimicrobial sensitivities be obtained for all isolates to monitor the possible development of resistant strains.[13] Finally, we recommended that an educational campaign emphasizing good personal hygiene be initiated at school assemblies and by the local news media.

To prevent future outbreaks, the importance of personal hygiene and proper methods of food preparation should be taught at schools and community events. Theoretically, in small towns experiencing endemic shigellosis, outbreaks may be prevented by cancelling community gatherings. Because enteric disease is ubiquitous and community gatherings have important social value, we recommend following basic hygienic measures rather than cancelling these events. In Alaska, potlatches could provide a good opportunity for education through posters, flyers, and information booths. Specifically, privately prepared foods served at community gatherings should be maintained at appropriate temperatures,[2,12] by keeping them either properly refrigerated or heated until consumption.

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Articles

Key Issues in Managed Competition

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All managed competition proposals for health system reform must confront several key issues. The premiums paid to health care purchasing cooperatives will need to be subsidized for those who cannot pay full fare; the amount and sources of the subsidies are controversial political issues. The payments passed on by purchasing cooperatives to health plans must be risk adjusted to account for differences in the health care needs of their enrolled populations. This is essential to create a level playing field for competition and to eliminate incentives for plans to use risk assessment for attracting enrollees. The data and methods needed for risk adjustment, however, are not adequate at present. The Clinton Administration's plan to limit expenditure increases raises a host of thorny issues. Maintaining quality of care will require health plan quality report cards to be supplemented by external quality assurance systems. Assuring quality will be particularly problematic for traditional indemnity plans. The structure and governance of the system, administration simplification, and other issues need to be addressed. The size and voluntariness of the purchasing cooperatives greatly influence all of these considerations. Physicians should inform their political representatives on how these issues should be resolved as compromise bills are drafted by the United States Congress this year.

(Shapiro DW: Key issues in managed competition. West J Med 1994; 160:434-439)

To contribute meaningfully to the debate about health care system reform, we need to understand how the proposed new systems might work. This is not easy. The formal proposals are complex, and they differ in important details. Three principal plans under consideration by the United States Congress include the Cooper bill (House of Representatives [HR] 3222), which would create purchasing cooperatives through which health insurance could be bought voluntarily; the Chafee bill (Senate 1770), which would achieve universal coverage with an individual mandate to purchase health insurance; and the Clinton plan (HR 3600), which would achieve universal coverage through an employer mandate and provide backup premium caps if cost-containment goals are not achieved.

In this article I examine some of the principal issues involved in how the various managed competition proposals would work. Except for caps on premium increases, which are used only in President Clinton's proposal, the issues discussed are relevant to all of the managed competition proposals being considered by the Congress. The discussion is divided into two broad topics: the flow of money into health care purchasing cooperatives and then to health plans; and the cost, quality, and value of care. I conclude with some special concerns that deserve attention as a managed competition system evolves.

Flow of Money to Purchasing Cooperatives and Health Plans

Health care purchasing cooperatives (called alliances in the Clinton plan) are the centerpiece of managed competition. They organize or manage the competition among the health plans participating in the cooperative. Some proposals would permit several cooperatives to coexist in one place, but the Clinton plan would require states to create one exclusive public cooperative in each geographic area. Participation in a cooperative could be mandatory or voluntary for consumers or businesses; the Clinton proposal would require every citizen to obtain health insurance through a cooperative, while under the Cooper bill participation in a cooperative is purely voluntary.

Cooperatives serve as intermediaries between consumers and health plans. A health plan that wishes to attract patients would submit a bid to a cooperative each year. In exchange for the per capita premium that it bids in advance, the plan would agree to provide the services in the basic benefit package to all who select the health plan (up to the limits of enrollment set by the plan). In effect, this gives individual consumers the purchasing power of a large group. Important issues must be resolved about how money is paid to cooperatives and then conveyed to health plans.

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The author thanks the staff of the Physician Payment Review Commission, on whose work this article relies; any errors are solely the responsibility of the author. The viewpoints and analysis expressed in this article should not be construed as representing those of any other person or organization.

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Subsidization of Premiums Paid to Cooperatives

The money that is sent to cooperatives can come from the same sources that pay for health care now: individuals, employers, and government. Not everyone will be paying full freight, however. The Cooper and Chafee bills, for example, would permit low-income persons to purchase care through cooperatives without paying the full premium themselves. The Clinton plan would limit the contributions of employers to 7.9% of their payrolls and less for some businesses with fewer than 75 employees. Part-time employees would have only a prorated share paid by their employers. Early retirees who do not yet qualify for Medicare would continue to pay their share of the premium of the health plan they select, but their former employers would be excused from paying the employer's share.

There will inevitably be a shortfall in the money collected by each cooperative compared with what health plans will need to be paid to provide health care to their enrolled populations. The size of this shortfall is unknown, and this has produced a lively debate. The estimates depend on the number of persons and employers who will not pay full shares, the size of their discounts, the success of managed competition in holding down cost increases, the scope of the basic benefits package, and the increase in the use of health care services by persons who will receive better coverage than they have now. This last item depends on whether and how fast universal coverage is attained and the extent to which other barriers to care are overcome. Estimates of these factors are necessarily uncertain. The Clinton plan has built into its estimates a 15% cushion to account for these uncertainties. The Chafee bill would delay the expansion of its voucher program for low-income persons if sufficient savings are not realized.

There are two ways for this shortfall to be made up, which are the same ways by which undercompensated or uncompensated care is paid for now. One is for government to make up part or all of the difference. All of the reform bills provide governmental assistance for low-income persons, raising the money in various ways. The federal government already subsidizes health care premiums by permitting tax deductions for them; the reform proposals all limit these deductions to varying extents. The Clinton plan also relies on an increase in the cigarette tax; cuts in the growth of Medicare and Medicaid; and projected savings from administrative simplification, managed competition, and expenditure limits. The amount of the federal subsidies would be capped.

The other technique of subsidization is for those able to pay full fare to pay extra—that is, cost shifting. The inclusiveness of the cooperatives affects the amount of cost shifting that is possible, unless there is a mechanism to shift dollars among cooperatives (as in the Cooper bill). The Clinton plan is the most inclusive of all the plans, exempting only the employees of some large corporations from participating in the public cooperatives. In addition, the Clinton plan would impose a 1% payroll tax on the large corporations that bypass the public cooperatives as an explicit shift of costs from corporate to public cooperatives.

Other proposals envision smaller, voluntary, or multiple cooperatives. Some of these may consist predominantly of persons who are less able to pay and who may require care of higher cost, as would be true of cooperatives located in inner cities. These cooperatives would require greater subsidies or they would not be able to purchase the same health care that better-off persons could. More-inclusive cooperatives would better ameliorate the marginalization of low-income and high-risk populations.

Risk Adjustment of Payments to Health Plans From Cooperatives

Cooperatives will not serve as simple conduits of premium payments to health plans. The amount of money paid into the cooperative's coffers by or on behalf of a person will rarely be exactly the same as the amount of money sent to a health plan to pay for his or her care. This is primarily because the premiums paid by individuals will be community rated (the average for the community), while payments to health plans must be risk adjusted. Risk adjustment is needed for two reasons: to provide a level playing field for competition, and to eliminate incentives for health plans to inappropriately "risk select" (try to influence the type of patients they attract to their plans).

Risk adjustment is essential to the success of managed competition. The populations actually enrolled by the health plans are likely to differ in health status and requirements for medical services. The payments made to each plan must be adjusted so that the plan will receive the funds it needs to provide proper care for its enrollees. If health plans were not paid enough for caring for high-risk patients, such as patients with the acquired immunodeficiency syndrome, they would either lose money through no fault of their own or they might be forced to skimp on necessary care. Conversely, erring in the other direction—overpaying for high-risk patients—might cause plans that care for healthier populations to be underpaid. In addition, consumers can better compare health plans if the plans each set their premium at what they would need to care for the average person in the cooperative. Health plans will only do this if they know they will be reimbursed adequately for whatever mix of patients they actually draw.

Inaccurate risk adjustment would give health plans incentives to try to enroll better-compensated persons and disenroll poorly compensated persons, as they do today. Insurers will probably not be permitted to deny coverage outright to high-risk persons, but there are many subtler ways in which health plans could try to influence the composition of their enrolled population. The geographic location of providers could discriminate powerfully among populations. Plans might gear their marketing toward healthier populations and erect roadblocks to care

for patients with chronic illnesses. Such activities would need to be monitored closely, such as by examining the reasons why people switch plans. It may prove difficult, though, to regulate plans' marketing strategies. If plans were paid appropriately for the risk profile of their enrolled population, incentives to risk select would be eliminated.

Unfortunately, adjusting accurately for risks is easier said than done.[1] Age, sex, health status and conditions, and past use of medical services can be used to predict future health care use to some extent. The problem is complicated because only efficient use of needed services (defined in some way) should be taken into account. In other words, it would be undesirable to pay either more or less than "necessary" for the differing health needs of health plans' populations—but it can be difficult to know what is necessary. Not all of the needed data for risk adjustment are available, and the American Academy of Actuaries recently concluded that risk adjustment formulas remain largely "untested" at the present time.[2]

It is not clear how much risk adjustment will be necessary—will plans attract populations of enrollees that differ in risk?—but to the extent that risk adjustment is needed, it will be vital to the success of managed competition. Risk adjustment would become less critical if actual health care use were factored to some degree into a cooperative's payments to health plans. This could be done either directly or through reinsurance or thresholds for outlier costs, but it would dilute the favorable incentives of prepaid (capitated) care.

It must also be decided whether risk adjustment should be done within cooperatives or across them, perhaps within entire states. Cross-subsidization among cooperatives would be immensely unpopular among those paying for the cost shifting, but it may be necessary to avoid perpetuating the differences between tiers of care that now exist. The smaller and less inclusive the cooperatives, the greater this problem becomes.

Cost and Value of Care

Combining Managed Competition With Expenditure Limits

Containing the rising cost of health care is a key goal of reform. The intent of managed competition is to bring market forces to bear on health care costs. The Clinton proposal supplements managed competition with expenditure limits (enforced as caps on premium increases) to ensure that the rate of growth of expenditures is reduced to the desired level. The premise of expenditure limits is that effective market competition may not be achieved in many areas of the country and that there are sufficient waste and inefficiency in the present system to provide at least one-time savings under the pressure of a budget cap before expenditures risk becoming too low. The question is in part a philosophical one: Is the government or the marketplace better able to set the "right" level of expenditures for health care? What is the "right" level?—what persons will pay for, or what is judged to be sustainable for the economy in the long run?[3]

Limiting expenditures involves three tasks: setting initial spending limits for each cooperative or state, determining the allowable increases in the limits each year, and enforcing them. Each task poses thorny issues. The problem in establishing the baseline limits for the first year is that per capita expenditures on health care vary greatly among regions and states. These variations are not well explained by differences in the cost of doing business—such as rent, salaries of office personnel, and malpractice insurance—or differences in the health needs of local populations.[1] To what extent should these existing patterns of spending be grandfathered into the initial limits? It would be undesirable to lock in existing inefficiencies or penalize those who are already providing care efficiently.

There are additional obstacles to setting initial expenditure limits based on historical spending patterns. Substantial inadequacies exist in the data on spending for all health services, and the baselines would need to be adjusted for border crossing, for persons not included in a cooperative, and for increased use by persons previously uninsured or with poor access to care. The problems are exacerbated if the limits are crafted for small cooperatives compared with states as a whole. There is time for much progress to be made, however, before the Clinton plan would begin the use of expenditure limits in 1996.

The alternative to the use of historical spending to set the baseline expenditure limits is to establish a common spending limit for all areas. The limits would need to be adjusted for differences in the cost of care beyond the control of providers, such as differences in practice costs (average commercial rents, utilities, and the like) or the health needs of populations. Although this approach is preferable in theory, in practice it would require dramatic cuts in spending levels in many regions—changes that could not realistically be accomplished in a short time.

Assuming that the system begins by grandfathering historical spending levels—as the Clinton plan does—the question then is whether and how fast to try to remove unwarranted spending variations among cooperatives and states. It would be desirable to develop some plan to do this over time so that the system as a whole becomes more efficient. The Clinton Administration proposes to create an advisory commission to recommend methods for doing this. Even without budgetary controls, effective competition might result in movement of the high-cost areas toward the benchmarks set by low-cost areas as health plans adopt the practices of the low-cost areas to gain a competitive edge.

Setting the target rates of increases in spending requires judgments about the desired long-term rate of growth in health care spending and how quickly the increases in health care costs can be brought down to that rate. The Clinton proposal sets the target growth rate for 1996 as the increase in the consumer price index during 1995, plus 1.5%. The target growth rate is reduced to the growth in the consumer price index alone by 1999. The strict limits for the first four years can be regarded as anything from necessary to utter fantasy, depending on the degree of slack that now exists in the health care system

and the new system's ability to cut costs without compromising necessary care. The increase in the consumer price index is usually less than the growth of the gross domestic product, and the major industrialized nations have rarely been able to keep the rate of growth of health expenditures below even that of the gross domestic product for a sustained period.[3] But the United States spends a much higher percentage of its gross domestic product on health care than do other nations, so it may well be possible to keep a tight rein on spending increases for a time.

Finally, what should be done when a cooperative's projected spending exceeds its budgeted target? The most direct way to ensure budgetary compliance is for the cooperative to reduce its payments to health plans (and providers) by the amount of the excess. Plans must live within the means provided them or go out of business. The Clinton plan relies on such premium regulation to ensure that budget targets are met, but there are choices involved in how this is done.

An initial determination must be made that a cooperative—or perhaps a state—is going to exceed its target for the upcoming year. This is done by multiplying the projected enrollment in each plan by the plan's premium bid. If the total exceeds the budget target, then the excess must be withheld from some plans. Which plans should be penalized: those with the highest premiums, or those with the highest rates of growth in premiums from the preceding year?

The Clinton plan proposes to withhold excess payments from those plans that increased their premiums by a percentage greater than that which the cooperative's budget was permitted to increase, without regard to the absolute level of the premium. Even the lowest cost or most efficient plan could be penalized if it raised its premium by more than the allowed percentage. This method would also create a perverse incentive for the level of the premium the plans establish in the first year: the higher the better.

The "percentage increase" approach has its advantages, too. It would maintain pressure on all plans to limit cost increases, not just the high-cost plans. It would tend to preserve initial variations among premiums of plans within a cooperative—variations that might be needed to make up for incomplete risk adjustment of payments to plans. If fee-for-service plans cost more, this would help them survive and thus preserve a pure fee-for-service option for consumers.

An alternative is to penalize the higher cost plans when the cooperative is projected to exceed its spending target. This would reinforce the incentives of managed competition and presumably increase the overall efficiency of health care. It would place greater stress on the accuracy of the risk adjustment mechanism, though, because high premiums that are needed to make up for incomplete risk adjustment would not be protected. In addition, a high-cost plan that was succeeding in controlling its costs might nevertheless be penalized.

These options are not exclusive: any combination of the two is possible, and the mix could be changed over time. The decision might rest on whether it is thought that health plans differ in cost because of inefficiencies or because they provide different levels of care, value, and amenities. If they provide different amenities, perhaps the differences should be maintained to respect consumer choice. It should also be noted that consumers are penalized indirectly if they select plans that end up having payments withheld to meet cooperative budget targets. Such persons must pay the full marginal amount (above the employer's contribution) of the high premium set by the plan, but the excess dollars will be withheld from the plan and used to reduce everyone's premium payments. Few consumers will want to have this happen to them two years in a row, unless they view the services the plan can provide for the limited amount of money it actually receives as worth the high premium.

There is an additional enforcement mechanism available for fee-for-service payments: regulation of the fee schedule payments to practitioners. Under the Clinton plan, each cooperative would establish a fee schedule (perhaps patterned after the Medicare fee schedule) for use with all fee-for-service payment. By regulating cooperative-wide or plan-specific conversion factors, total expenditures could be controlled either prospectively or retrospectively. A variety of technical issues need to be settled concerning how this would work and how it would relate to premium regulation.[1]

A market alternative to strict spending limits might be for cooperatives to set limits on increases but enforce them only for the employers' contribution. Cooperatives would pay to health plans the full amount of any budget-busting premiums that consumers elect to pay. This would sharpen the incentive for consumers to choose any plan that kept its premium below budget, because they would be paying any budget-exceeding component of the premium directly from their own pocket. If competition worked, increases in health spending over the budget could be interpreted as "worth it" to the public.

Quality of Care

Information about quality of care is important for consumers to consider in choosing health plans. The managed competition proposals envision a quality report card that consumers can use to compare health plans' performances on specific quality measures. The specific measures would need to be developed and refined, but the concept is an extension of trends already at work in the health care market.

Report cards have potential disadvantages. Health plans might focus their resources on specific indices on the report card and permit other, less easily measured aspects of quality of care to deteriorate. It may be difficult for consumers to evaluate and compare the varying combinations of strengths and weaknesses of different plans on the 50 or so measures that may be used. Perhaps weighted summaries could be developed for enrollees with particular types of health needs—healthy young couples with children, for example. Further, it will often be necessary to adjust a plan's performance on a specific

measure to take into account factors not under the plan's control, such as characteristics of that plan's enrolled population that might affect the quality measure. This is especially important for outcome measures, but such adjustments have not yet been developed. It is important that only valid measures that can be interpreted by consumers be used in the report cards.

High-quality care is said to cost less; nevertheless, there is the potential for cost pressures to lower the quality of care. To supplement the quality report cards, externally mandated quality assurance systems are necessary. The respective roles of the federal government, states, cooperatives, and other organizations in monitoring and improving quality need to be defined. The requirements for fee-for-service plans are problematic: Should they be held to the same standards as managed care plans? By what means can they monitor and improve fee-for-service physicians' quality of care? What is certain is that practitioners and plans will be required to produce greater amounts of detailed clinical and other quality data than they do now.

Improving the Value of Care

Perhaps one of the most important goals of health care reform is to raise the value received for the resources the nation devotes to health care. This requires connecting the benefits of treatment with its costs in a way that permits both to be considered when decisions at all levels are made.

Managed competition proposals seek to do this in several ways. First, they limit the tax deductibility of health insurance, so that consumers face at least the full marginal cost of the coverage they purchase. The Cooper plan would limit the tax deduction to the premium for the lowest cost plan, so that anything more than this is paid for with after-tax dollars. The Clinton plan would require employers to pay at least 80% of the weighted average premium of the cooperative; consumers would pay with after-tax dollars the difference between the employer contribution and the actual premium charged by the plan they select. This would have the effect of magnifying the cost differences among plans in terms of consumers' out-of-pocket share of the premium. Assuming an employer pays 80% of an average premium, an employee would pay twice as much for a health plan that has premiums that are 120% of the average compared with one with average premiums.

Second, managed competition gives health plans an incentive to meet the health needs of their members more efficiently. Health plans can do this by providing individual services more efficiently and by finding more effective and cheaper means to treat a given condition. In addition, the expected benefits and risks of a treatment course vary among patients, so there is a spectrum of declining returns for providing the service. Along that spectrum, health plans may select different thresholds for providing a treatment. To the extent that these differences among health plans can be communicated to consumers and are reflected in the level of the premium, consumers will be able to make their own choices about the value they wish to obtain for their health care dollars. But many of these differences will necessarily remain unappreciated by consumers (as is the case today), which would hinder the ability of consumers to compare plans accurately on value. There is also a risk that the gaps between tiers of care may grow too large.

Finally, value will also be influenced by coverage decisions. Expenditures on new technologies and services are a principal component of the rise in health care costs, in part because they are often used when their benefits are uncertain or small. Managed competition would give health plans an incentive to adopt only those technologies and procedures that have been demonstrated to be effective and of good value. A case can be made that a federal board should make some coverage decisions.[1,4] The criteria, structures, processes, and legal environment for such decisions need to be clarified.

Additional Considerations

Many other important issues on health care reform are not discussed here. The ideal structures and governance of managed competition systems are not known. In addition to functional and administrative considerations, the issues include the distribution of power and accountability throughout the system. All of the plans would standardize billing, but the savings may be overwhelmed by the additional data requirements that will be imposed on providers. To the extent that freedom of choice of provider is maintained and physicians care for patients enrolled in more than one plan, the need for physicians to understand and comply with the data, quality, coverage, and other requirements of many organizations may increase rather than diminish.

As the details of the system are being debated, some broader concerns should be kept in mind. The reform will have important implications for the nature and future of fee-for-service medicine. The fee-for-service sector is likely to continue to shrink and may remain available for only the well-to-do. On the other hand, many persons place great stake on having a fee-for-service option, and President Clinton's legislative proposal requires all health plans to permit out-of-plan care on a fee-for-service basis with a higher copayment. The distinctions between the out-of-plan option, preferred provider networks, and pure fee-for-service plans remain to be worked out: in the Clinton plan, the only difference seems to be in the amount of copayment required. The need to control the rate of growth of volume and intensity of care may necessitate as-yet-unforeseen changes in aspects of fee-for-service practice. It is hoped that the various types of managed care organizations, too, will change to better meet the needs of patients and providers.

The roles and future of Medicare and Medicaid need to be determined. Should their beneficiaries be integrated into the managed competition system, and if so, should it be done immediately or over time? What problems would this create? The Cooper bill would eliminate Medicaid, and the Chafee and Clinton proposals would retain it. Ac-

cess to care for certain populations will require special attention. Undocumented aliens would not be covered under the managed competition plans. Even under universal coverage, inner-city residents and others may still face barriers to obtaining high-quality care. How can their special needs be met in the context of managed competition? Providing care for these vulnerable groups that is comparable to that provided to the general public will require extra money. Some may resist paying for these costs, particularly for illnesses considered to be a result of risk-incurring behavior rather than random chance.

Finally, the demand for and the nature of primary and specialty care are likely to change. The trend toward the increased use of primary care gatekeepers is likely to continue, although it would be desirable for health plans to develop innovative ways of using specialists that would achieve high quality at reasonable costs. Teaching hospitals will face new challenges as they compete on equal terms for patients and as the number and types of residency programs change. Citizens will need to become more informed about the quality and cost of their health care. Lifestyle-associated illness may become a greater issue as costs become increasingly scrutinized.

It should be clear that the key issues involved in crafting a managed competition system have not been resolved. Interested groups have an opportunity to help formulate a system that reflects their perspectives on how the system could work best. It is incumbent on health professionals to play a major role in devising and leading the new system.

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* * *

BURNING OUT

First you lose respect for the limbs,
then abdomen, then lungs and heart,
and, ultimately, you're happily hacking at brain
in search of your corpse's pituitary stalk.

Years later, you suddenly realize that
your breast exams are faster than your speech.
Position sense, vibration, hot and cold,
the cranial nerves have gone the way of the fundus:
a willing suspension of recognition.

Soon your exam consists of senseless pokes
at the pannus of the belly and knee jerks,
which will be next to go.

Words like "fremitus" and "pectoriliquy" float
like clouds on the surface of a river headed out
to join the differential of pheochromocytoma
and the faces of forgotten patients.

No wonder you rise later and later each year.
No wonder you stare at your face in the mirror
every morning before shaving.

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Conferences and Reviews

New Insights Into Mechanisms of Immune Glomerular Injury

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Based on a paper presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 1993

Although glomerular disease remains the most common cause of end-stage renal disease worldwide, major advances have been made recently in understanding the cellular and molecular mechanisms that mediate these disorders. The nephrotic syndrome in noninflammatory lesions such as minimal change or focal sclerosis and membranous nephropathy results from disorders of the glomerular epithelial cell that can be simulated in animal models by antibodies to various epithelial cell membrane epitopes. Clarification of how these antibodies affect epithelial cells to induce a loss of glomerular barrier function should substantially improve understanding of the pathogenesis of minimal change or focal sclerosis. In membranous nephropathy, proteinuria is mediated primarily by the C5b-9 complex through similar mechanisms that also involve glomerular epithelial cells as targets.

Inflammatory glomerular lesions are induced by circulating inflammatory cells or proliferating resident glomerular cells. Understanding of how these cells induce tissue injury has also evolved considerably over the past decade. Neutrophil-induced disease involves leukocyte adhesion molecules in regulating neutrophil localization; proteases, oxidants, and myeloperoxidase in mediating injury; and platelets in augmenting these processes. The activated mesangial cell exhibits altered phenotype and proliferation with the release of oxidants and proteases. Mesangial cell proliferation may be initiated by basic fibroblast growth factor and is maintained by an autocrine mechanism involving platelet-derived growth factor. Transforming growth factor β is important in the subsequent development of sclerosis.

(Couser WG: New insights into mechanisms of immune glomerular injury. West J Med 1994; 160:440-446)

Major advances in the basic sciences of immunology, cell biology, and molecular biology over the past decade have led to major new insights into the pathogenesis of kidney diseases. In this review I focus on current understanding of immunologic glomerular diseases, emphasizing insights derived from recent studies, particularly as they relate to clinical glomerular diseases. In reviewing this area, I focus primarily on the mechanisms that cause acute rather than chronic progressive disease and particularly on proteinuria as a marker of glomerular injury.* I further divide the mechanisms of glomerular tissue injury into those that are associated with inflammatory changes by light microscopy and those that are noninflammatory in nature. The major pathways of injury as they are currently understood are depicted schematically in Figure 1. More detailed reviews of this subject have been published elsewhere.[1-3]

*See also the editorial by D. H. Lovett, MD, "Immunologic Glomerular Disease—New Prospects for Specific Therapy," on pages 481-482 of this issue.

Noninflammatory Mechanisms of Glomerular Injury

Two major glomerular diseases occur in which glomerular permeability is massively increased in the absence initially of any alterations in glomerular structure. These are minimal change or focal sclerosis and idiopathic membranous nephropathy. The glomerular lesions in both these diseases can be closely simulated in animal models in which the principal site of immune attack is the glomerular epithelial cell.

Glomerular Injury Due to Non-Complement Fixing Antibodies to Glomerular Epithelial Cells

The pathogenesis of minimal change or focal sclerosis is unknown. There is now increasing evidence, however, that the nephrotic syndrome results from glomerular effects of circulating permeability factors probably derived from immunocompetent cells. Thus, hybridomas of immunocompetent T cells from patients with active mini-

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ABBREVIATIONS USED IN TEXT

Ig = immunoglobulin
PDGF = platelet-derived growth factor
SPARC = secreted protein acidic and rich in cysteine

mal change disease secrete a factor that can transfer a similar lesion to rats, whereas supernatants from T-cell hybridomas of patients in remission have no such factor.[4] With the use of a new technique that permits the direct measurement of changes in albumin permeability in isolated normal glomeruli, patients with active focal sclerosis evidenced by the recurrence of disease in renal transplants have been found to usually exhibit a serum factor that can induce an increase in albumin permeability.[5] It is unclear whether these two techniques for measuring nonimmunoglobulin permeability factors are measuring the same substance, and the precise characterization of these factors awaits further study. The ability to detect such factors in a clinical setting may represent a major advance in understanding the pathogenesis and treatment of these disorders.

Although these circulating permeability factors are not immunoglobulins, lesions that closely simulate the structural and functional features of minimal change or focal sclerosis can be induced in animals by various antibodies that have in common the ability to bind to the membrane of glomerular epithelial cells without fixing complement. These antibodies, which include some antiglomerular antibodies,[6,7] anti-Fx1A $F(ab')_2$,[8] and monoclonal antibodies K9/9[9,10] and 5-1-6,[11] all induce a dramatic change in the shape of the epithelial cells, accompanied by areas of detachment of epithelial cells from underlying glomerular basement membrane.

A better understanding of how these antibodies cause glomerular injury will likely also clarify how nonimmunoglobulin permeability factors damage glomeruli as well. These models provide the opportunity to conduct such further studies. Possible mechanisms include stimulation of the release by glomerular epithelial cells of materials that directly damage underlying glomerular basement membrane, such as oxidants[12] or proteases,[13,14] or interference with molecules that regulate cell-matrix

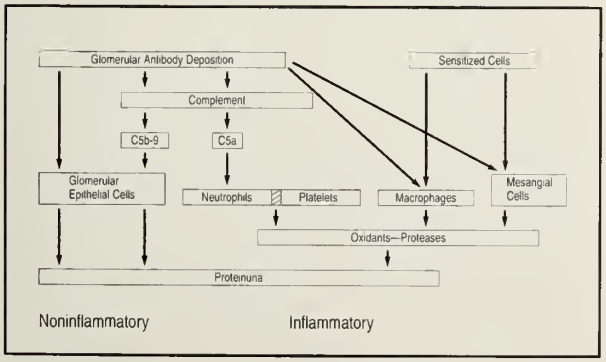

Figure 1.—The schema depicts the established mechanisms of immune glomerular injury that lead to proteinuria (modified from Couser[3]).

interaction leading to cell detachment from the basement membrane,[15,16] or both. Much has been learned recently regarding the molecular mechanisms that regulate the adherence of glomerular epithelial cells to basement membrane, and disorders of these processes may be particularly important in the pathogenesis of noninflammatory types of injury in diseases such as minimal change disease.[16] Detachment is a common underlying feature of many experimental glomerular diseases involving the epithelial cell as a target of injury. Detachment itself may increase protein excretion through glomerular hemodynamic changes, including loss of the hydraulic conductivity barrier and increased water flux that produces enhanced bulk flow of macromolecules, including proteins, through the capillary wall.[17,18]

Glomerular Injury Induced by Complement Fixing Antibodies to Glomerular Epithelial Cells and C5b-9

The prototype of C5b-9-induced glomerular injury in human disease is membranous nephropathy.[19-22] Like minimal change or focal sclerosis, the initial glomerular lesion in membranous nephropathy is also a totally noninflammatory one. In membranous nephropathy, however, there are extensive subepithelial deposits of antibody and complement components including C3 and C5b-9.[22] Although the nature of the deposited antibody in human membranous nephropathy has not yet been established, many other aspects of the immunopathogenesis of the disorder are now understood based on studies of the Heymann nephritis models in rats that closely simulate the human lesion. In Heymann nephritis, subepithelial immune deposits result from antibody binding to antigens on the surface of glomerular epithelial cells, the best characterized of which is GP330 localized in the clathrin-coated pits.[23] Antibody binding to the epithelial cell membrane induces complement activation, probably through the alternative complement pathway.[24] Because the deposits form only on the outer, or subepithelial, surface of the glomerular capillary wall, complement- and immunoglobulin-derived chemotactic and immune adherence proteins are not interactive with circulating cells, probably accounting for the noninflammatory nature of the lesion.[25] Proteinuria, however, is a complement-dependent phenomenon and appears to be mediated primarily by the C5b-9 membrane attack complex of complement (reviewed by Couser and co-workers[19,21]).

Evidence for this derives from studies in intact animals, isolated perfused kidneys, and, recently, isolated glomeruli. In intact animals, selectively depleting C6 with a monospecific antibody abrogates the formation of the C5b-9 complex without other known biologic effects.[26] When rats are given experimental membranous nephropathy by the passive administration of anti-Fx1A antibody (passive Heymann nephritis), C6 depletion has no effect on glomerular antibody deposition but totally abrogates C5b-9 formation in glomeruli and the development of proteinuria.[26] In isolated perfused rat kidneys, the same anti-Fx1A antibody induces proteinuria within 60 min-

utes when all components of the C5b-9 complex are present, but fails to do so in the absence of C6 or C8.[27] Similar results have now been obtained in isolated glomeruli where anti-Fx1A antibody induces a pronounced increase in albumin permeability in the presence of serum that has all components of the C5b-9 complex, but fails to do so in the absence of C6 or C7.[28]

The mechanism by which C5b-9 causes proteinuria is still unclear. Like the permeability factors discussed earlier, the effect of C5b-9 in membranous nephropathy is on the glomerular epithelial cells, where the binding of antibody specific for epithelial cell membrane antigens induces complement activation. Freeze-fracture studies demonstrate the insertion of C5b-9 into the glomerular epithelial cell membrane.[29] In non-nucleated cells, this leads to pore formation and osmotic lysis. In nucleated cells, defense against complement attack is present in the form of complement regulatory proteins such as C8 binding protein and CD59, and sublytic C5b-9 attack may serve instead to activate cells. In glomerular epithelial cells, sublytic C5b-9 attack induces increased intracellular calcium, the activation of phospholipase C, increased levels of inosine phosphorylase 2 and 3, diacylglycerol, and phosphatidic acid and the release of arachidonic acid, prostaglandin $F_{2\alpha}$, and thromboxane.[30-32]

This process of glomerular epithelial cell activation by noncytotoxic C5b-9 attack may lead to the release of mediators that directly damage glomerular basement membrane such as oxidants[33] or proteases.[14,33] Current evidence would support epithelial cell oxidant release as the most likely mechanism. Thus, recent evidence of increased oxidant production by glomerular epithelial cells in experimental membranous nephropathy following C5b-9 attack in vivo has been presented,[35] and the treatment of rats with antioxidants such as dimethyl thiourea substantially reduces proteinuria without reducing antibody deposition or complement activation.[36]

Another possible effect of sublytic C5b-9 is on glomerular epithelial cell attachment to basement membrane. Some studies suggest that proteinuria in membranous nephropathy occurs in areas of detachment.[37,38] Although the cell adherence molecules that regulate glomerular epithelial cell detachment have not been fully identified, epithelial cells appear to express primarily $\alpha_3\beta_1$ and $\alpha_5\beta_1$ integrins,[38,39] and antibody to $\alpha_5\beta_1$ inhibits attachment to laminin, fibronectin, and collagen by 80% to 90% in vitro.[38] Both antibodies to glomerular epithelial cells and C5b-9, perhaps acting through the release of oxidants or proteases, may induce alterations in cell matrix attachment proteins or their ligands that facilitate cell detachment. The apparent increase of antiadhesive proteins such as *s*ecreted *p*rotein *a*cidic and *r*ich in *c*ysteine (SPARC) in C5b-9-mediated epithelial cell injury may also facilitate this process.[40]

Although C5b-9 may participate in inducing the basement membrane thickening and spike formation that characterizes chronic membranous nephropathy, evidence that this is so is less clear. In vitro, C5b-9 produces an increase in type IV collagen,[41] but it has not been shown to have a demonstrable effect on the production of or gene expression for laminin, the principal constituent of the thickened glomerular basement membrane.[42] In vivo increases in laminin and type I collagen gene expression are partially complement-dependent in experimental membranous nephropathy, but type I collagen is not a major constituent of the glomerular scarring in this disease.[42]

Inflammatory Mechanisms of Glomerular Injury

Most types of glomerulonephritis exhibit striking changes by light microscopy, particularly hypercellularity that may reflect infiltration by circulating inflammatory cells such as neutrophils, monocytes, or platelets or the proliferation of resident glomerular cells, particularly mesangial cells. Examples would include postinfectious glomerulonephritis, immunoglobulin (Ig) A nephropathy, rapidly progressive glomerulonephritis, lupus nephritis, and membranoproliferative glomerulonephritis. A plethora of recent studies establishes that both circulating inflammatory cells and resident glomerular cells can mediate glomerular injury acutely by the release of oxidants, proteases, and probably other chemoattractant and glomerular basement membrane-degrading molecules. Ongoing injury is also augmented by the release of various cytokines and growth factors that result in an increased deposition of extracellular matrix, leading to scarring and sclerosis. The following is a brief summary of recent observations in this area.

Neutrophils

In any setting where antibodies induce complement activation or immunoglobulin deposition at sites accessible to circulating inflammatory cells—such as subendothelial or mesangial immune complex deposits—neutrophil infiltration occurs early.[13,43] It has been known since the 1960s that neutrophils cause much of the antibody-induced injury that follows.[44] Recent studies have substantially clarified how neutrophils localize in glomeruli through interaction with a variety of leukocyte adhesion molecules (selectins, integrins, intercellular adhesion molecules, and vascular cell adhesion molecules) that are displayed on cell surfaces.[45,46] Many of these molecules are induced or overexpressed in response to cytokines and other inflammatory mediators. It has also been recently established that neutrophils localized in glomeruli induce injury by undergoing a respiratory burst that results in the release of toxic oxygen metabolites, particularly hydrogen peroxide.[13] Hydrogen peroxide is nephritogenic by virtue of its ability to interact with neutrophil-derived myeloperoxidase.[47-49] Myeloperoxidase is a cationic molecule that localizes in glomeruli by interacting with negatively charged (anionic) sites and interacts with hydrogen peroxide and a halide to form hypohalous acids that directly damage the glomerular basement membrane.[47-49] It has also been shown that neutrophil-derived proteases such as elastase and cathepsin G, in physiologic concentrations, can induce a notable increase in glomerular permeability without accompanying structural dam-

age.[50] Even more recently it has been appreciated that in some settings platelets are not only essential for the occurrence of neutrophil-mediated injury, they apparently augment this process. The nature of this platelet-neutrophil interaction is still under study.

Macrophages

Macrophages are also present in the early cellular infiltrate in several different inflammatory glomerular lesions.[51-53] Unlike neutrophils, they may localize in response to cytokines derived from both cell-mediated and antibody-mediated immune reactions. The presence of macrophages may reflect an initial T-cell infiltrate and be part of a cell-mediated immune reaction that can occur in the absence of antibody deposition.[52] Alternatively, macrophages may be localized through a variety of chemotactic and immune adherence mechanisms to cause tissue injury, like neutrophils, by the release of oxidants and proteases.[54] Macrophages have been shown to be the principal effector cells in some types of chronic immune complex diseases.[55] Unlike neutrophils, macrophages can also contribute to injury through the release of tissue factor that facilitates both intracapillary fibrin deposition and extraglomerular fibrin deposition leading to crescent formation.[56-58] Finally, macrophages are a potent source of transforming growth factor β, a cytokine that is now thought to play a central role in stimulating the production of extracellular matrix by both glomerular and interstitial cells leading to sclerosis and fibrosis.[59-61]

Lymphocytes

The cellular component of the immune response is an important mediator of several autoimmune diseases (reviewed by Waksman[62]). The limited experimental data available on this important mechanism in glomerular disease are well reviewed elsewhere.[51,63] T cells have been clearly shown to mediate hypercellularity independent of antibody deposition in rats[64,65] and chickens[66,67] and appear to participate in the recruitment of macrophages in some models of macrophage-mediated injury.[68,69] A recently described model of glomerulonephritis induced by immunization with myeloperoxidase provides good evidence that cellular immune mechanisms can mediate a glomerular vasculitis similar to that associated with antimyeloperoxidase antineutral cytoplasmic antibodies in humans.[70]

Platelets

Although the role of platelets in glomerular thrombosis has long been appreciated, recent studies have established a role for them in both neutrophil-mediated and mesangial proliferative glomerulonephritis.[71] We noted that the platelet is a prominent component of glomerular injury induced by neutrophil-dependent mechanisms involving oxidant injury and have recently shown that selectively depleting platelets in a neutrophil-mediated model of subendothelial immune complex nephritis essentially abolishes neutrophil-induced proteinuria without altering glomerular localization of antibody, complement, or neutrophils.[72] Studies using platelets labeled with indium 111 have shown that platelet accumulation occurs immediately in this model, within ten minutes of antibody deposition, and is dependent on complement but not on neutrophils.[73] These findings imply that a functional interaction takes place within the glomerulus itself between the neutrophil and the platelet and that this interaction is required for neutrophil-mediated injury to occur. The nature of this interaction has not been defined. The more recently identified role of platelets as mediators of mesangial cell proliferation in models of mesangial proliferative glomerulonephritis is described in more detail in the following section.

Mesangial Cells

Much attention in recent years has focused on the role of the mesangial cell in mediating both immune and nonimmune types of glomerular injury.[74-76] Mesangial cell proliferation is a prominent feature of glomerular diseases including IgA nephropathy, lupus nephritis, some types of steroid-resistant nephrotic syndrome, and other lesions. Because of the relative ease with which mesangial cells can be grown in vitro, a large amount of literature has developed to document the activation of mesangial cells by various inflammatory mediators including C5b-9, certain types of immune complexes, endotoxin, and various other cytokines and growth factors.[75] Additional in vitro studies demonstrate that the activation or proliferation of mesangial cells can lead to the release of a host of proinflammatory materials including oxidants, proteases, prostaglandins, growth factors, and extracellular matrix components.[76]

To initiate studies of the mechanisms that regulate mesangial cell proliferation in vivo, a model of mesangial proliferative glomerulonephritis in rats induced by administering antibody to the Thy 1.1 antigen on the mesangial cell membrane was used. In this antithymocyte serum model, antibody and complement induce an initial mesangiolysis followed by glomerular proliferation that is maximal five days later.[77] Cell proliferation can be accurately quantitated using a stain for the proliferating cell nuclear antigen, a nuclear protein expressed during the late G1 to G2/M phase of the cell cycle.[77] Immunohistochemical colabeling techniques documented that more than 85% of proliferating glomerular cells were mesangial cells as assessed by labeling of cells positive for proliferating cell nuclear antigen with antibody to Thy 1 or to α-smooth muscle actin, a protein expressed de novo by the activated mesangial cell in vivo.[77,78]

A prominent feature of the antithymocyte serum model is an early platelet influx into capillary loops and mesangial areas.[77,79] One of our initial questions was whether the platelet infiltration might somehow mediate the mesangial cell proliferation that followed it. Selective platelet depletion studies showed more than 70% reduction in mesangial cell proliferation in platelet-depleted animals.[77] (Complement depletion also prevented cell proliferation, apparently by markedly reducing the glomerular platelet influx, a previously unrecognized role for the complement system in glomerular injury.[80])

We then hypothesized that the mechanism of this platelet-mediated mesangial cell proliferation might involve the release of growth factors. Based on in vivo studies, platelets are known to produce a number of growth factors that can stimulate mesangial cell proliferation in vitro, including platelet-derived growth factor (PDGF), interleukin-1, epidermal growth factor, insulinlike growth factor type 1, and transforming growth factor β (in low concentrations).[81] We elected to initiate our studies of growth factor effects on mesangial cell proliferation in vivo with PDGF. Platelet-derived growth factor has been well documented by several laboratories to stimulate mesangial cell proliferation in vitro.[82] Using immunohistochemical techniques, we were able to show a substantial increase in mesangial cell production of both PDGF B chain and PDGF receptor β-subunit at three and five days in the antithymocyte serum model.[83] Moreover, when molecular techniques were used, a considerable increase in gene expression for both PDGF A and B chains and PDGF receptor β-subunit was shown in whole glomeruli at three and five days.[83] In situ hybridization studies localized the increase in PDGF B chain messenger RNA to mesangial areas.[84] The time course of detectable increases in both PDGF and PDGF receptor protein and messenger RNA corresponds closely with the course of mesangial cell proliferation in vivo.[83,84] Moreover, maneuvers that blocked mesangial cell proliferation including platelet and complement depletion also blocked these increases in PDGF and its receptor.[83]

In total, our studies provided strong circumstantial evidence in support of the hypothesis that PDGF was indeed an important mediator of mesangial cell proliferation in vivo. Two more studies were needed to confirm this, however. In the first, we attempted to reproduce mesangial cell proliferation by infusing PDGF into the renal artery in vivo. Infusing recombinant PDGF resulted in only modest mesangial cell proliferation in normal rats. If, however, rats were treated with small doses of antithymocyte serum that produced no detectable disease alone, infusing similar doses of PDGF resulted in a much more dramatic mesangial cell proliferation and glomerular hypercellularity.[85] Finally, attempts were made to block mesangial cell proliferation in the antithymocyte serum model by employing a neutralizing antibody to PDGF. To our surprise, we found no effect of PDGF blockade at two days, but a dramatic (60%) reduction in cells positive for proliferating cell nuclear antigen at four days.[86] Our studies thus suggest that PDGF is probably not the principal growth factor that initiates mesangial cell proliferation. Rather, PDGF, probably derived primarily from the mesangial cell itself and not from platelets, contributes to maintaining glomerular hypercellularity in this model by an autocrine mechanism involving mesangial cell stimulation of not only the growth factor but also its receptor.[87,88]

The series of observations summarized above establishes an important role for PDGF in glomerular disease. The demonstration of increased PDGF expression in several proliferative glomerular lesions in humans suggests that these observations are probably relevant in the clinical setting as well.[89] Clearly there are several other growth factors and cytokines that also participate.[75,90] In our laboratory we have begun to look at other factors that may be more important than PDGF in initiating mesangial cell proliferation and found an increase in the release of mesangial cell-derived basic fibroblast growth factor, an intracellular growth factor that can stimulate normal mesangial cells to proliferate in vitro and may be important in initiating this process in vivo.[91] We have also wondered what terminates the autocrine-driven maintenance phase of mesangial cell proliferation that leads to disease resolution. We have studied the role of SPARC in this process. This glycoprotein, which can bind to and neutralize PDGF, is also made by mesangial cells and might be increased as mesangial cell proliferation ensues.[92] Obviously these observations, rather than being answers to the questions posed, are initial steps on what is likely to be a long but, we hope, fruitful journey.

Our studies have also shown that mesangial cell proliferation precedes the increase in gene expression for several normal extracellular matrix components that may contribute to eventual sclerosis, not only in the antithymocyte serum model,[93] but in nonimmunologic progressive glomerular lesions such as the remnant kidney model[94,95] and diabetes mellitus.[96] Not only is matrix synthesis increased, but so, too, are the synthesis and release of a mesangial cell-derived neutral protease with basement membrane-degrading properties.[97] Moreover, a reduction in mesangial cell proliferation induced with antibody to PDGF also affects a reduction in matrix component deposition[86] similar to that seen with reagents that block transforming growth factor β.[58,98]

Conclusion

As understanding of the mechanisms of immune glomerular injury evolves, numerous new therapeutic strategies can now be devised, including agents that block or inhibit complement effects, oxidants, proteases, growth factors, and other cytokines. Appreciation of the role of several natural inhibitors of these mechanisms may also allow therapeutic manipulations that increase the production of regulatory proteins with a consequent therapeutic benefit. Thus, these changes in the basic understanding of the mechanisms of glomerular disease are likely to translate into new and more specific and effective forms of therapy in the next decade.

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Neuromuscular Complications of Human Immunodeficiency Virus Infection and Antiretroviral Therapy

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At least 4 distinct peripheral neuropathy syndromes occur in patients infected with the human immunodeficiency virus. The most common, painful sensory neuropathy, may be related to the viral infection or may be medication induced and is treated symptomatically. The other 3, chronic inflammatory demyelinating polyradiculoneuropathy, mononeuropathy multiplex (some patients), and the progressive polyradiculopathies related to the acquired immunodeficiency syndrome, may all respond to appropriate therapy. Both inflammatory myopathy and zidovudine myopathy also abate with early diagnosis and treatment.

(Miller RG: Neuromuscular complications of human immunodeficiency virus infection and antiretroviral therapy. West J Med 1994; 160:447-452)

Peripheral neuropathy has been reported in as many as 16% of patients with the acquired immunodeficiency syndrome (AIDS).[1-3] The severity of symptoms varies greatly, and the reported incidence is likely to be underestimated,[2] particularly in light of recent studies showing that many patients with AIDS have subclinical peripheral neuropathy.[4]*

Clinical Features

The presenting symptom of the mainly sensory neuropathy of AIDS is paresthesia. Most patients notice numbness or tingling in the toes that gradually spreads proximally and later involves the fingers. The sensory symptoms are usually symmetrical and develop insidiously, evolving over weeks to months. The dysesthesias may be burning and constant or associated with the lancinating pain of neuralgia; they are most noticeable in the feet and often hamper the patient's ability to walk, in some cases even more than weakness. Myalgia is less common, but cramping of the intrinsic foot muscles and the calves may be prominent and interfere with sleep, reflecting the propensity for partially denervated muscles to cramp.[5] Unsteadiness and increased fatigue while walking may develop in patients who have distal weakness.

Polyneuropathy is also well recognized as a complication of treatment with didanosine (2′,3′-dideoxyinosine, or DDI) and zalcitabine (2′,3′-dideoxycytidine, or DDC). These drugs are potent inhibitors of the human immunodeficiency virus (HIV) in vitro. Didanosine has little bone marrow toxicity, and its use is increasing in patients who cannot tolerate zidovudine. The drug inhibits HIV reverse transcriptase and suppresses HIV replication by blocking the synthesis of viral DNA. Painful neuropathy developed in 8 of 37 patients treated for more than 55 days in one study.[6] The neuropathy appears to be dose-related (especially in doses of more than 12 mg per kg per day). The incidence of peripheral neuropathy was substantially lower in another series for reasons that are unclear.[7] In all instances there is some tendency for improvement after the drug therapy is discontinued, but the reversibility is variable. Less information is available about zalcitabine, but it also produces a distal sensory neuropathy that is dependent on the dose and duration of treatment.[8,9] In a recent study of 11 patients who took zalcitabine for more than five weeks, a painful sensory neuropathy developed in 9 that appeared abruptly and involved the feet much more than the hands. Five patients had to stop zalcitabine treatment because of the neuropathy.[10] Neuropathies may also appear in patients receiving vincristine sulfate, isoniazid, ethambutol hydrochloride, rifampin, and dapsone.

Distal Symmetric Peripheral Neuropathy

Distal symmetric peripheral neuropathy is the most common presentation among patients with generalized neuropathies.[1,3] Distal areas of skin in the lower extremities may show trophic changes, such as hair loss, thinning of the skin, and in more advanced cases, pedal edema and a dusky rubor that is particularly striking when the limbs are dependent. In most cases, weakness is mild and af-

*See also the editorial by D. K. Ziegler, MD, "Human Immunodeficiency Virus and the Peripheral Nerves," on pages 482-483 of this issue.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
CSF = cerebrospinal fluid
EMG = electromyogram/electromyographic
HIV = human immunodeficiency virus

fects only the intrinsic foot muscles. Tendon reflexes are sluggish or absent at the ankles and usually normal at the knees and in the upper extremities. Distal sensory loss begins in the toes and gradually spreads proximally; abnormalities are noted in the fingers when the sensory symptoms have risen to midcalf. There is usually equal impairment of all modalities of sensory function.

Chronic Inflammatory Demyelinating Polyradiculopathy

The Guillain-Barré syndrome may be associated with HIV seroconversion, or it may be the presenting feature of HIV infection.[11] Chronic inflammatory demyelinating polyradiculopathy is clinically similar to Guillain-Barré syndrome and different from distal peripheral neuropathy (Table 1). The former, however, is rarely an acute illness, usually being subacute or chronic in patients with AIDS or AIDS-related complex, and the abnormalities of the autonomic nervous system that are conspicuous in Guillain-Barré syndrome are generally absent.[11] Weakness is usually found in both distal and proximal muscles of the upper and lower extremities. Tendon reflexes are generally sluggish or absent. Distal sensory abnormalities are often mild compared with the weakness. Patients with severe generalized weakness may have facial diplegia, bulbar weakness, and respiratory insufficiency.

Mononeuropathy Multiplex

Mononeuropathy multiplex is less common than demyelinating polyradiculopathy or distal peripheral neuropathy. Patients report a mononeuropathy of relatively abrupt onset, and then additional mononeuropathies develop. Demyelinating polyradiculopathy may also cause patchy weakness or sensory loss, but these deficits always evolve gradually. Cranial nerve involvement is common in patients with mononeuropathy multiplex.[12]

TABLE 1.—*Clinical Characteristics of Patients With Distal Symmetric Peripheral Neuropathy (DSPN) and Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)**

Characteristic	Patients Affected: DSPN, % (No./No.)†	Patients Affected: CIDP, % (No./No.)†
AIDS	92 (48/52)	19 (3/16)
AIDS-related complex	8 (4/52)	82 (13/16)
Sensory > motor	80 (28/34)	6 (1/16)
Motor > sensory	6 (2/34)	87 (14/16)
Abnormal cerebrospinal fluid	13 (6/48)	93 (13/14)

AIDS = acquired immunodeficiency syndrome

*From Miller et al.[1]
†Number of patients with given clinical characteristic versus the number with neuropathy.

When mononeuropathy multiplex occurs in patients with AIDS-related complex, it is usually benign and self-limiting, but in those with advanced AIDS, it may be caused by cytomegalovirus (CMV) and require treatment with ganciclovir.[13,14]

Progressive Polyradiculopathy

Subacute progressive sensory and motor loss involving the lumbar and sacral roots may develop in patients with AIDS (Table 2). The radicular deficits are usually contiguous and relentlessly progressive. Early impairment of urinary bladder and rectal sphincter control and sacral sensory loss are the distinctive features of this progressive polyradiculopathy. There are usually no long-

TABLE 2.—*Clinical Features of Cytomegalovirus Radiculopathy**

Feature	Patients, No. With Feature/ No. With Radiculapathy
AIDS	7/7
Progressive severe weakness	7/7
Early sacral paresthesias	7/7
Early urinary retention	7/7
Retinitis	3/7
Sensory level	2/7
Pyramidal signs	0/7

AIDS = acquired immunodeficiency syndrome

*From Miller et al.[15]

tract signs. Weakness, sensory loss, and tendon areflexia spread rostrally throughout the lumbar and thoracic segments to the cervical and cranial segments. In a growing number of cases, both the neuropathologic findings and cultures of cerebrospinal fluid (CSF) have implicated CMV.[15]

The differential diagnosis of progressive polyradiculopathy includes lymphomatous infiltration of nerve roots, neurosyphilis, mass lesions (especially tumor or epidural abscess), and chronic inflammatory demyelinating polyradiculopathy. Two patients with HIV infection have also had clinical features typical of motor neuron disease.[16] The cause of this condition remains unclear.

Natural History

Subclinical polyneuropathy is clearly present in a substantial percentage of patients with HIV infection.[4,17,18] These patients for the most part have a mild distal peripheral neuropathy. The course of these peripheral neuropathies is variable; spontaneous improvement or stabilization of the deficit has been documented in a number of these patients.[18,19] In general, chronic demyelinating polyradiculopathy tends to progress slowly, although the symptoms may be severely exacerbated by opportunistic infection. Distal peripheral neuropathy appears to be more variable; spontaneous remission, stabilization, and relentless progression have all been observed.

The first five patients whom we saw with progressive polyradiculopathy and five patients whose cases were reported previously[15,20,21] all died of pneumonia or respiratory failure within several weeks of onset.

Electrophysiologic Studies

In patients with distal peripheral neuropathy, compound muscle action-potential amplitudes in the distal lower extremities are diminished.[1] The conduction velocities and distal latencies are, for the most part, normal or within 20% of normal, indicating an axonal neuropathy.

By contrast, patchy pronounced slowing of nerve conduction has been found in all patients with chronic demyelinating radiculopathy.[1,11] Prolonged or absent F responses and prolonged distal motor latencies are common; slowing of motor nerve-conduction velocity in the forearm or the leg is observed frequently.

The electrodiagnostic results in patients with mononeuropathy multiplex usually show multifocal axonal changes, generally without findings suggesting demyelination. Early in the course of progressive polyradiculopathy, all electrophysiologic studies are normal except the electromyogram (EMG), which reveals a reduced recruitment pattern in weak muscles. As the disorder progresses, the evoked muscle action-potential amplitudes decrease and fibrillations appear, compatible with axonal degeneration.[15]

Laboratory Features

Serum polyclonal immunoglobulin levels are elevated in most patients with AIDS-related peripheral neuropathies.[22] None of our patients have had a monoclonal gammopathy.[23] The erythrocyte sedimentation rate may be elevated, sometimes markedly so. All patients tested had antibodies to HIV.

The CSF is abnormal in about 90% of patients with chronic demyelinating radiculopathy but normal in patients with distal symmetric peripheral neuropathy unless there is coexistent disease.[11] Pleocytosis is often seen in patients with chronic polyradiculopathy.[11,22] The lymphocyte count may be increased as much as 50×10^9 per liter (50 per mm^3). Pleocytosis above that level requires a vigorous search for a coexistent process, such as lymphoma or infection. The CSF protein level is often elevated, especially in patients with demyelinating radiculopathy, but may be normal in patients with distal peripheral neuropathy. Elevated levels and increased synthesis of immunoglobulin G have been observed, particularly in patients with demyelinating radiculopathy.

In progressive CMV polyradiculopathy, the CSF appearance is striking (Table 3), with polymorphonuclear pleocytosis, hypoglycorrhachia, and pronounced elevation of the protein content.[15,21] Cultures of CSF grew cytomegalovirus in four of seven patients (all of whom died of this disease), and in some patients blood and urine specimens also contained the virus. Cultures were negative for bacteria, fungi, parasites, and other opportunistic pathogens. The cerebrospinal fluid VDRL test was negative in all patients.

The sural nerve on biopsy examination is usually abnormal, especially in patients with chronic demyelinating polyradiculopathy and those with mononeuropathy multiplex. Inflammation is frequently conspicuous in both the epineurium and the endoneurium and usually is especially prominent near small blood vessels.[12,24] Inflammatory responses are observed in both chronic polyradiculopathy and distal symmetric neuropathy, but they are usually more intense in the former. There is a predominance of $CD8^+$ (cytotoxic/suppressor) cells in the inflammatory response.[24]

TABLE 3.—*Laboratory Features in Patients With Cytomegalovirus (CMV) Radiculopathy*

Labaratary Test	*Results*	
	Mean	*Range*
Cerebrospinal fluid		
Leukocyte count, cells × 10^9/liter (/mm^3).....	0.4 (449)	0.03-1.5 (29-1,500)
Polymorphonuclear leukocytes, fraction of 1 (%).....	0.71 (71)	0.58-0.94 (58-94)
Protein, grams/liter (mg/dl)...	2.74 (274)	1.13-6.30 (113-630)
Glucose, mmol/liter (mg/dl) ..	1.6 (29)	0.8-2.6 (15-47)
		Patients, No. Positive/No. Tested
Culture positive for CMV		4/7*
VDRL		0/7
CMV at autopsy		5/5
Acute denervation†		7/7
Small evoked M waves‡		7/7

*Cerebrospinal fluid cultures were positive for CMV in 4 patients, and in 1 other, the urine culture was positive.

†Electromyographic evidence of fibrillations, positive waves, and reduced recruitment, most pronounced in caudal myotomies.

‡Evoked M-wave (muscle action potential) amplitudes in foot muscles were reduced, with normal conduction velocity.

Immunologic Aspects

The similarity of the clinical, histologic, and electrophysiologic features of HIV-related demyelinating polyradiculopathy to those encountered in Guillain-Barré syndrome, experimental allergic neuritis, and demyelinating polyradiculopathy not associated with HIV infection suggests a similar pathogenesis.[25] Humoral immune factors have been implicated in both Guillain-Barré syndrome and experimental allergic neuritis because serum from affected patients or animals caused peripheral nerve demyelination.[26,27]

Both HIV and CMV have been cultured from peripheral nerve in patients with AIDS and peripheral neuropathy.[28,29] Viral infections may alter peripheral nerve antigens, triggering an autoimmune response. The presence of a variety of antiviral antibodies and autoantibodies may lead to immunologic cross-reactivity. Imunologic cross-reactions involving putative autoantigens have been implicated in the pathogenesis of a number of autoimmune diseases of the nervous system.[30] An antigen present in natural killer cells has been shown to be identical to, or highly cross-reactive with, antibodies to a myelin antigen.[30] Recently neuroleukin, a lymphokine and growth factor that affects specific areas of both the central nervous system and the peripheral nervous system, has been found to have a region homologous to gp 120, an HIV envelope glycoprotein[31,32]; gp 120 markedly decreases the trophic effect of neuroleukin.[32] Conceivably either gp 120 or cross-reactive antibodies could contribute to a reduc-

tion in the binding of neuroleukin to target neurons. These observations and the fact that in many patients inflammatory neuropathies improve with plasmapheresis and intravenous immune globulin administration suggest that immunologic mechanisms play a key role in the pathogenesis of at least some of these conditions.

Treatment

In a recent study of HIV-positive patients with chronic inflammatory polyradiculopathy, spontaneous improvement occurred occasionally, but the improvement usually followed treatment with steroids or plasmapheresis.[11] Prednisone treatment is effective in patients with this syndrome who do not wish further plasmapheresis. Whether the treatment of HIV-related demyelinating polyradiculopathy with prednisone alone is effective, safe, and practical is still uncertain. Other immunosuppressive drugs must be used cautiously in these patients. Plasma exchange therapy has been effective in treating patients with idiopathic disease[33] and polyradiculopathy associated with paraproteinemia[19,21,34] or HIV infection.[11,35,36] The use of intravenous immune globulin, 400 mg per kg per day for five days, has also produced improvement in some patients.[37-40]

Although most patients with progressive polyradiculopathy have died, several patients with this syndrome improved greatly after early treatment with ganciclovir.[15] The main factor appeared to be early diagnosis and treatment. In patients whose condition improved, treatment was initiated within 48 hours of the initial presentation rather than waiting as long as 12 days for CSF cultures, as had been done in previous patients. We initiate induction therapy with ganciclovir, 2.5 mg per kg intravenously every eight hours for ten days.[15] Maintenance treatment is then undertaken with 5 to 7.5 mg per kg of ganciclovir five days per week. Ganciclovir is an acyclic nucleoside analogue similar in structure to acyclovir. The drug has potent in vitro activity against human CMV retinitis and gastrointestinal disease. It penetrates the blood-brain barrier, and CSF concentrations are 40% to 50% of plasma concentrations. Peak concentrations appear to be substantially higher. Long-term suppressive therapy is usually needed because of the high incidence of relapse, at least in patients with retinitis, after therapy is discontinued. Dose-related decreases in neutrophil and leukocyte counts are the most common side effects.

Therapy for patients with distal symmetric peripheral neuropathy is conservative and symptomatic. Medications are given for neuropathic pain (amitriptyline hydrochloride or desipramine hydrochloride), and patients with substantial distal weakness are fitted for ankle-foot orthoses.

Treatable Myopathies

Treatable primary muscle disorders associated with HIV infection include inflammatory myopathy[41-45] and zidovudine myopathy.[46-51] The diagnostic features of these treatable conditions are reviewed to aid early therapeutic intervention.

Zidovudine Myopathy

More than 40 patients have had a necrotizing myopathy related to the use of zidovudine (previously called azidothymidine, or AZT).[50,51] Almost all have had AIDS, and all were taking zidovudine for many months (9 to 30 months). Myopathy may also occur in patients taking lower doses (500 mg per kg per day). Insidiously progressive muscle weakness was the most common presenting symptom. Myalgia was prominent, usually exacerbated by exercise. Weakness involved both the pelvic and shoulder girdles. Facial and neck muscles were not involved. Serum creatine kinase levels were elevated in all patients, ranging from 2 to 11 times normal. Electromyograms showed early recruitment of brief, small, polyphasic motor unit potentials, mild-to-moderate fibrillation, and positive sharp-wave activity.[50]

Abnormal features on muscle biopsy specimens include scattered polygonal and angular atrophic fibers undergoing granular degeneration and regenerating and necrotic fibers with phagocytosis. "Ragged-red fibers" indicative of abnormal mitochondria were also seen.[51] There was no nemaline rod formation. In 11 of 18 cases, focal endomysial or perimysial (or both) mononuclear cell inflammatory infiltrates were present. There was no vasculitis or fibrosis. The finding of "ragged-red fibers" in some patients and the ultrastructural evidence of abnormal mitochondria in almost all biopsy specimens,[51] as well as the recent finding that more than 80% of the DNA of muscle mitochondria is depleted,[52] suggest that zidovudine use produces a mitochondrial myopathy.

After stopping zidovudine therapy, myalgia resolved in two to three weeks in all who had this symptom. Most patients returned to normal or nearly normal strength. Strength did not begin to improve until four to six weeks after discontinuing zidovudine and improved slowly but steadily over the next few months. Creatine kinase levels returned to normal in all patients with notable improvement except one. Follow-up EMG studies disclosed either disappearance or a substantial reduction of fibrillation wave activity.

The speed and completeness of recovery was inversely correlated with the severity of weakness at the time of the diagnosis. Myalgia resolved rapidly (often within 2 weeks), and strength improved more gradually (6 to 20 weeks). Patients with severe weakness had improvement but did not fully recover, again underscoring the need for early diagnosis. Reducing the dose of zidovudine was of no value clinically. Recovery began only when the drug was completely stopped.[50,53] After notable improvement, some patients have resumed treatment with quarter- or half-dose zidovudine with no further worsening clinically, although myalgia recurred in two patients. No myopathy has yet been described with the use of didanosine or zalcitabine.

Inflammatory Myopathy

Numerous reports have described inflammatory myopathy in association with HIV infection.[41-45,54,55] Most patients present early in the course of HIV infection. Some

reports are complicated by simultaneous therapy with zidovudine, but myopathy has developed in many patients who have had no exposure to the drug. All had moderately severe, painless progressive weakness involving both the shoulder and pelvic girdle muscles with no dysphagia or neck muscle weakness. Creatine kinase levels were elevated, and EMG disclosed active myopathy. All had substantial inflammation on muscle biopsy, with both nemaline rods and a selective loss of thick filaments on electron microscopy. Many patients have improved with treatment with either prednisone alone or prednisone plus plasma exchange. The use of intravenous immune globulin may also prove to be helpful for this condition. The particular risks of corticosteroid use in patients with HIV infection are still not entirely clear.[56,57]

Differential Diagnosis

The most important element in establishing the diagnosis of zidovudine myopathy is the clear-cut lessening of myalgia and improved strength when the drug is stopped. The following clinical features are seen in patients with zidovudine myopathy:

- Progressive proximal muscle weakness;
- Exercise-exacerbated myalgia in thighs and calves;
- AIDS;
- Full-dose zidovudine therapy for more than nine months;
- Elevated creatine kinase levels;
- Myopathy on EMG with fibrillations in proximal muscles;
- Necrotizing myopathy on muscle biopsy with little inflammation and no nemaline rods; and
- A decrease in myalgia and improvement in strength, creatine kinase levels, and EMG findings 6 to 12 weeks after discontinuing zidovudine.

These findings differ in five important respects from treatable inflammatory myopathy. With the inflammatory myopathy:

- Patients are often HIV-positive, but do not meet diagnostic criteria for AIDS;
- Patients are often not taking zidovudine;
- The condition is rare;
- The biopsy specimen displays prominent inflammation, widespread nemaline rods, and a selective loss of thick filaments;
- Patients respond to treatment with plasma exchange and prednisone.

There is still no evidence of direct HIV infection of muscle cells, although this has been seen with infection with the human T-lymphotropic virus type 1.[58] Antigen to HIV was, however, localized to a large number of perivascular macrophages within the endomysium of a muscle biopsy from a patient with inflammatory myopathy related to HIV infection.[59] Thus, infected macrophages may be important in the pathogenesis of this myopathy, which is probably an autoimmune response initiated by HIV.

Thus, two treatable primary muscle diseases may complicate HIV infection. Unfortunately, it is not possible in every case to confidently determine the cause of muscular weakness.[60] Part of the problem is that generalized weakness and wasting are common in patients with AIDS, and histologic abnormalities in muscle may appear much more frequently than was previously supposed.[61,62] Nonetheless, it is possible in almost all cases to distinguish between zidovudine myopathy and the inflammatory myopathy complicating HIV infection. Histologic findings were of great importance in distinguishing these two different myopathies. Considerable inflammation and nemaline rods were seen only in the inflammatory group, but a necrotizing myopathy was typical of the group taking zidovudine. These findings suggest that early diagnosis is feasible and of great importance to ensure an optimal therapeutic response.

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Epitomes

Important Advances in Clinical Medicine

Radiology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in radiology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Positron Emission Tomography in Clinical Oncology

THE BEST IMAGING METHODS available for the diagnosis and monitoring of neoplasms are magnetic resonance imaging (MRI) and computed tomography (CT), with both procedures based on tissue structure and relying heavily on contrast enhancement for differential diagnosis. While MRI and CT can provide precise anatomic delineation of such lesions, as well as determine changes in tumor volume in response to therapeutic manipulation, they cannot rapidly assess therapy response when changes in treatment planning could be most effective—that is, before changes in tumor volume occur. In addition, little or no information is provided that could be used to predict response to therapy other than referral to the knowledge of the natural history of similar lesions once the diagnosis has been made.

Because the early detection of primary or metastatic neoplasms and rapid therapeutic intervention are major clinical goals, new techniques that can be used to diagnose, provide prognostic information, and assess response to therapy are needed. A new technology, positron emission tomography (PET), is beginning to provide such information. Positron emission tomographic imaging techniques are now extending the ability to differentiate tissues based on functional or biochemical characteristics.

Positron emission tomography is being used in a variety of specialties, including cardiology, the neurosciences, and oncology. In the field of oncology, fludeoxyglucose F 18 (^{18}FDG), a glucose analogue, has been the most widely used radiotracer for the study of tumors. The PET-^{18}FDG technique has been evaluated by investigators at several institutions. For primary brain tumors, this technique can distinguish high-grade from low-grade lesions and radiation necrosis from residual or recurrent tumor, it can detect malignant degeneration in tumors originally low grade in nature, and it can provide metabolic information regarding tumor biochemistry and response to therapy not achievable using morphologic imaging techniques. Whole-body imaging of cancer with PET-^{18}FDG is now done at many centers across the country. Cancers routinely studied at most clinical PET centers include those of brain, breast, colon and rectum, head and neck, liver, lungs, and lymphoma, melanoma, and musculoskeletal tumors. Most of the reported sensitivities, specificities, and accuracies of PET applications in these cancers are 80% or greater. Exciting new areas for PET imaging include ovarian, thyroid, pancreatic, and renal cancers.

Positron emission tomography provides information about in vivo regional chemistry with sensitivity and specificity comparable to those obtained by radioimmunoassay studies of body fluids, and it can often detect abnormalities before structural changes have occurred. As gross changes in anatomy are no longer adequate end points for therapy protocols, treatment need no longer be based on clinical response, structure of the lesions, and histopathologic examination of biopsy specimens. In vivo biochemical characterization of tumors with labeled tracers is becoming a new method for classifying tumors and for planning and monitoring their treatment. In vivo assessment of the metabolic activity of tumors, specifically DNA synthesis, protein synthesis, and fatty acid and glucose use is proving useful for both diagnosing and monitoring the effects of therapy on tumors. Positron emission tomography makes it possible to measure the rate of use of substrates such as glucose and amino acids that supply energy to tumors or nucleotides that reflect DNA metabolism. It also provides pharmacokinetic and pharmacodynamic data concerning radiolabeled cancer chemotherapeutic agents. With PET, the exploration of the kinetics of cellular processes is providing a "biologic resolution" not heretofore achieved with other imaging methods.

Adjuvant metabolic tumor imaging studies complement the morphologic evaluation of human cancers. In clinical practice, these techniques are being used to assess the effectiveness of surgical therapy, radiation therapy, and chemotherapy and can document the extent of tumors and progression or regression in response to different forms of treatment. These data permit modifications of the treatment plan sooner than can be determined by the clinical response of patients or changes in lesion structure. Imaging will permit the study of biochemical processes where they occur and perhaps detect changes indicative of tumor response to therapy before alterations in structures occur. In the future, it is likely that multiple PET radiotracers, along with multimodality imaging, will be used for the diagnosis and monitoring of the effects of therapeutic intervention. The rationale for this lies in part with the heterogeneous nature of cancer and the need to evaluate multiple biochemical indicators in order to classify lesions and assess their response to treatment.

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Use of Magnetic Resonance Imaging in Sports Injuries

THE UNIQUE SOFT TISSUE CONTRAST capabilities of magnetic resonance imaging (MRI) make it a good tool for evaluating sports injuries. With increasing experience, specific indications for using MRI have emerged. In general, whenever surgical procedures are seriously considered and the diagnosis is not entirely obvious, MRI should be used. Some surgeons will use MRI to exclude a pathologic disorder when clinical suspicion is low and the likelihood of finding an abnormality during an operation is also low.

In many cases of knee injuries, physical findings are not specific and MRI may define the abnormality. Magnetic resonance imaging is greater than 90% sensitive and specific for detecting meniscal tears and may define tears best treated with primary meniscal repair. Anterior and posterior cruciate ligament tears are also accurately defined by this method. Magnetic resonance imaging may also define trabecular bone injuries that are not diagnosed by x-ray films. With continued unrestricted weight bearing, these fractures may progress to injury of the subchondral bony plate with irreversible injury of the overlying cartilage. In complex knee injuries, MRI may detect the full spectrum of findings, which may include injuries to the menisci, cruciate, and collateral ligaments and the bone. Cost-efficacy studies have shown MRI of the knee to decrease costs without adversely affecting the results of treatment.

When properly done, MRI is the only technique that can determine the degree of rotator cuff injury as well as diagnose complete tears. Standard MRI may detect labral tears, and MR arthrography may be the best test currently available to evaluate shoulder instability.

In the foot and ankle, MRI is used to define occult bone injuries in patients with persistent pain with normal plain films. Tendon or ligament disruption, plantar fasciitis, and Achilles tendon tears may also be demonstrated with MRI. Magnetic resonance imaging can influence the choice of therapy for Achilles tendon tears by differentiating between complete and partial tears. Abnormalities of the subtalar joint and sinus tarsi may also be defined. Finally, muscular strains, tears, and hematomas can be routinely defined with MRI. Thus, this technique is unique in its ability to evaluate a broad spectrum of musculoskeletal injuries noninvasively.

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Spiral Computed Tomography

SPIRAL COMPUTED TOMOGRAPHY (CT), also called helical or volumetric CT, has re-energized the field of computed tomography and presented a challenge to magnetic resonance imaging in many situations. The technologic advance from conventional CT to spiral CT might be compared with the development of motion pictures from still photography: whereas conventional CT acquires a single image in a discrete plane of section before a patient is moved to a new location for a second picture, spiral CT collects anatomic information quickly and continuously as the patient is moved through the scanner.

Speed has at least three advantages. Evaluation time is decreased so that patients who are unstable (such as trauma patients) or those who may have difficulty remaining still (such as very young or very old patients) are better served. Spiral scanning of the chest can be finished in as little as 24 seconds. Regardless of the patients' condition or age, speed helps minimize the effect of movement artifact that can hinder diagnosis. In the lungs, conventional CT can miss nodules that are less than 10 mm when a patient takes a different depth of inspiration between two adjacent slices. By comparison, spiral CT images are collected during a single breath-hold so that inconsistencies in a patient's breathing do not cause a nodule to move out of the imaging plane, especially at the lung bases where metastases often occur.

Perhaps most important of all, fast scanning also enhances the use of intravenous contrast media. If spiral scanning is begun soon after a bolus of contrast medium is administered intravenously—through an 18-gauge catheter—the arterial vasculature is selectively enhanced and the images can be reconstructed to resemble conven-

tional arteriograms. Pathologic conditions detected by "CT angiography" include carotid artery stenosis, renal artery stenosis, and bypass graft occlusion. Spiral scanning during the brief period of peak organ enhancement improves the detection of several tumors—for instance, those of the liver—and the delineation of their extent. Spiral CT may also decrease the amount of contrast medium required and thus reduce the cost of examinations at busy hospitals by $1 million per year.

Spiral CT is also superior to conventional CT in that it produces an anatomically continuous set of data, instead of discontinuous slices of anatomy. With the volume of data that is acquired, a patient's anatomic features can be reconstructed and displayed in any plane without the "step artifact" seen with conventional CT. Three-dimensional reconstructions can also be done to facilitate surgical planning in cases that involve complex anatomic relationships, such as with temporal bone. Unlike conventional CT, additional images can be reconstructed retrospectively at any level or with any section thickness without additional irradiation or scanning time. For example, after spiral scanning is completed with 8-mm interscan spacing, a pulmonary or hepatic lesion can be placed in the center of a CT section so that volume averaging is minimized and more reliable density measurements can be taken. Moreover, the original data can be used to reconstruct images with only 4-mm interscan spacing, thus increasing the number and confidence with which lesions less than 1 cm are detected.

Spiral CT represents a genuine breakthrough in body imaging, enabling rapid and continuous scanning of large anatomic areas during a single breath-hold. The volumetric information that is generated allows a great deal of flexibility in reconstructing images to answer the diagnostic question posed by each patient. For these reasons, spiral CT has rapidly become the method of choice for most thoracic and abdominal CT scanning applications.

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Ultrasonography of Foreign Bodies

THE SOLE OF THE FOOT is one of the most frequent sites of foreign body penetration. Not all foreign bodies are detectable with x-ray films. Although most glass fragments are well seen in plain films, wood fragments and plastics are more difficult and are likely not to be visible on roentgenography.

Ultrasonography is sensitive in detecting glass, metal, wood, and plastic foreign bodies in superficial soft tissues. The most important sonographic consideration in their detection is the use of a high-resolution transducer of 7 to 10 MHz, preferably a linear array, focused in the near field of view. Suspected small or tiny fragments need high resolution for detection. The examination is done in two perpendicular planes.

On ultrasound examination, a foreign body will usually produce a bright hyperechoic interface and an accompanying acoustic shadow, the size of which will depend on the size of the surface of the retained object. Glass is intensely hyperechoic. Wood absorbs sound to cast a shadow. Metal, such as a needle fragment, causes a typical comet-tail pattern.

An important advantage of sonography in the detection of foreign bodies is the mobility of the unit, as it can be taken to emergency departments or patients' bedsides. Sonographic localization during the surgical extraction of a foreign body diminishes tissue damage and shortens the procedure. If surgical removal is contemplated, the overlying skin is marked where the shortest pathway exists, and once identified, the depth from the surface to the object is measured. During sterile procedures for foreign body removal, the transducer is sheathed with a cover to maintain sterility. Sterile acoustic gel or sterile saline solution is used as the couplant on both sides of the sheath. The sheath protects the sterile field and allows appropriate visualization. During surgical removal, if the object is deep in the soft tissues, a needle can be introduced to mark the path with ultrasound guidance to the position of the foreign body.

Not all bright, intensely echo-producing areas seen in soft tissues are foreign bodies. Air bubbles or calcifications are highly reflective. Sometimes a keratotic skin lesion can also mimic a superficial foreign body.

Within the abdomen, ultrasonography can be used to identify retained surgical sponges that produce bright hyperechoic foci with prominent acoustic shadowing. Other foreign bodies that have been identified with sonography are surgical clips and prosthetic grafts, ingested pills in the stomach, vascular and biliary stents, ureteral and vesical stents, breast implants, intrauterine contraceptive devices, vascular and vesical catheters, and intraocular foreign bodies. An expanding literature reports the sonographic visualization of catheter fragments in the vascular system, including the heart, and in some cases the retrieval of the foreign object by ultrasonographic guidance. Although bullets and shrapnel are best identified with radiography, ultrasonography has been used to localize and retrieve these missiles in limited circumstances. In these instances, ultrasonography has been an adjunctive study to the primary imaging modality.

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Altered Fractionation in Radiation Therapy for Head and Neck Cancer

RADIATION THERAPY, alone or in combination with other treatment methods (such as surgical therapy), has been a standard treatment of cancer of the head and neck. A "conventional" course of curative radiation therapy has typically been a single daily dose of 180 to 200 cGy five days a week to a total of 6,600 to 7,200 cGy in 33 to 40 fractions over 6½ to 8 weeks. It has also been "hypofractionated" into as few as 1 to 24 fractions (usually ≥250 cGy) one to four times a week or "hyperfractionated" into as many as 40 to 80 fractions, giving multiple fractions in one day. Because hypofractionated regimens with curative intent have been fraught with both poor control rates and formidable complications, they are not generally recommended. Therefore, the rest of this discussion will concern hyperfractionation.

Two important radiobiologic principles support the use of hyperfractionated radiation therapy. First, the occurrence of long-term side effects—severe soft tissue fibrosis or necrosis—depends more on the size of each individual fraction than on the final total dose. A fraction size of 450 cGy can cause much more long-term damage than a fraction size of 180 cGy, even when the former is used in a course of treatment to the same or lower total dose. In addition, substantial biologic and clinical evidence shows that these fractions should be separated by approximate six-hour intervals to allow for sufficient repair of the long-term effects. Therefore, the total dose can be escalated higher than the conventional 6,600 to 7,200 cGy by treating with a smaller fraction size (less than 180 cGy). This is accomplished by treating twice a day to totals as high as 8,160 cGy. Acute mucosal or skin reactions remain unchanged, however, and actually may be more severe than with conventional radiotherapy.

Hyperfractionated regimens may be accelerated so that a total dose is completed in a shorter period than conventional radiotherapy. For instance, a regimen of 6,600 cGy may be completed in 5 weeks rather than 6½ to 8 weeks. This accelerated therapy counteracts tumor repopulation that can be an important factor in local failure. Just as in pure hyperfractionation (without being accelerated), long-term side effects are reduced, although acute mucosal or skin reactions are increased. Nearly all hyperfractionated regimens have incorporated some degree of acceleration. This can range from 110 to 160 cGy per fraction given twice a day to a total dose of 6,720 to 8,160 cGy over 6 to 7 weeks to 140 to 150 cGy per fraction given three times a day to a total of 5,040 to 5,400 cGy in 12 days. Three prospectively randomized studies have used hyperfractionation and have shown considerably improved local or regional control and complete response rates. One study has also shown notably improved disease-free and overall survival rates for the hyperfractionated group, and a second also showed a trend in survival improvement. Results of altered fractionation (hyperfractionation or accelerated hyperfractionation) have been promising and have gained acceptance, especially in the treatment of moderately advanced to advanced head and neck cancer.

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Captopril Renography for the Detection of Renovascular Hypertension

RENOVASCULAR DISEASE is an uncommon but important cause of hypertension. It is important because correcting the underlying disease can result in permanent cure and help preserve renal function. The prevalence of renovascular hypertension depends on several clinical risk factors. In patients with mild hypertension, the prevalence is probably less than 0.5%. It increases to about 5% to 15% in patients with severe hypertension, especially if the hypertension is refractory to standard therapy, the patients are young, are smokers, have an abrupt onset of hypertension, have an abdominal bruit, or have other evidence of vascular disease. In such patients a noninvasive test with good sensitivity and specificity has the highest clinical likelihood of ruling in or ruling out renovascular disease.

Until recently an isotope renogram using radioiodinated iodohippurate sodium (Hippuran) or technetium Tc 99m-labeled diethylenetriaminepentaacetic acid (DTPA, or technetium Tc 99m pentetate) was the screening test, but moderate specificity led to a substantial number of false-positive results. Thus, if the prevalence of disease is about 10% and the specificity is 70%, the positive predictive value of an abnormal test is only 25%. The introduction of captopril renography has increased both the sensitivity and specificity of the test, making it an almost ideal noninvasive screening test. The test involves an oral dose of a short-acting angiotensin-converting enzyme (ACE) inhibitor, usually captopril, in a dose of 25 to 50 mg. This medication causes a fall in glomerular filtration in the kidney supplied by an artery with a functionally notable stenosis. Either ^{99m}Tc pentetate or ^{99m}Tc mertiatide (mercaptoacetyltriglycine) can be used as the radiopharmaceutical agent. The uptake of the radiopharmaceutical in an abnormal kidney is slower and the maximum uptake in that kidney is seen later than in normal kidneys. One approach is to complete a captopril renogram first and, if it is normal—that is, there is no asymmetry in perfusion and excretion between the kidneys—no additional testing is required. Renovascular hypertension is excluded with a high degree of confidence (90% to 95%). When there is asymmetry with reduced glomerular filtration and an increased transit time on one side, we repeat the study with

the patient off ACE inhibitors. If the second study shows a return to normal, that strongly suggests that a functional stenosis is present. We advise patients to stop taking diuretics before the test, but not all investigators agree that this increases the diagnostic value.

Several series are comparing this functional imaging study with the gold standard, which is the correction of hypertension when the stenotic lesion is treated either by angioplasty or surgical repair. Based on several studies, sensitivity and specificity are both around 90% to 95%. It is noteworthy that renal arteriogram is not considered the gold standard because there can be stenotic lesions that are not functionally important. Nevertheless, contrast arteriography is an essential part of evaluation in those patients who have an abnormal captopril renogram and who are candidates for surgical correction.

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Managing Hickman Catheter Problems Without Surgery

HICKMAN CATHETERS are commonly used for long-term central venous access. These catheters are usually inserted through the subclavian vein and then tunneled for stability and to prevent infection. As with any central venous line, complications are encountered in both placing and maintaining the patency of this catheter. These complications include catheter malposition, intraluminal thrombosis, and occlusion of the catheter tip by a fibrin sheath. These problems can often be managed with nonoperative, fluoroscopically guided manipulations.

The most common problem after a Hickman catheter is successfully inserted is malposition of the catheter tip. This occurs most frequently into the ipsilateral internal jugular vein. Extension from the right subclavian vein into the left subclavian through the brachiocephalic vein may also be observed. Repositioning the catheter tip into the superior vena cava is generally not difficult. This is accomplished by inserting a catheter into the femoral vein. This catheter is guided fluoroscopically into the upper thorax through the venous system. The catheter tip is positioned cephalic to the Hickman line and then deflected caudally with a tip-deflecting wire. In most cases, the Hickman line will be pulled into proper position as the angiographic catheter is pulled away.

To avoid problems with catheter malposition, many physicians prefer that central venous lines be placed by an interventional radiology team, where suitable fluoroscopic imaging and catheter-inserting skills are readily available. Moreover, ultrasonographic guidance may be used to direct the venous puncture, reducing the chance of inadvertent subclavian arterial puncture, which can be associated with bleeding complications. In addition, if a complicating pneumothorax develops, it can be recognized and evacuated immediately without awaiting a postprocedural chest x-ray film.

Thrombosis of the central line may also be managed successfully in most cases. Instilling 50,000 to 100,000 units of urokinase will frequently lyse the occluding thrombus. If this is unsuccessful, directing an angiographic guide wire under fluoroscopic observation will often dislodge the thrombus.

An encasing fibrin sheath at the catheter tip causing line occlusion is a more difficult problem to manage. Two techniques have been used to approach this problem. The first involves placing a wire with a tight J tip through the catheter, stripping the fibrin from the tip. The second method is to insert a femoral venous catheter and manipulate an encircling snare around the Hickman catheter. As the snare is pulled caudally, the fibrin sheath is peeled away from the central venous line. Using this method, a 95% success rate in restoring patency and function has been reported.

Interventional radiologic techniques are effective in preserving the long-term patency of Hickman catheters and obviate the need for surgical replacement in most patients.

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Three-Dimensional Spiral Computed Tomographic Angiography

THREE-DIMENSIONAL SPIRAL computed tomographic (CT) angiography is a new technique for obtaining images of the vascular system noninvasively. Unlike conventional CT scanners, spiral computed tomography combines continuous tube rotation with a continuous table feed. This allows a region of the body to be studied during a single breath-hold, thus eliminating most motion and respiratory artifacts. A volumetric data set can be acquired that can be timed with an intravenous bolus during either the arterial or venous phase of the injection for abdominal studies. The arterial phase starts about 15 to 20 seconds after the start of the intravenous injection. Once the data set is acquired, it is edited to obtain three-dimensional images of the vascular system. Editing eliminates overlying soft tissues and bony structures, producing a "subtraction angiogram" with either a shaded surface display or maximal intensity projection format.

To date, the most common clinical indications for three-dimensional spiral CT angiography include evaluation of the abdominal aorta and its branches, the pul-

monary arteries, the carotid artery bifurcation, and the circle of Willis. Technical factors need to be adjusted for each region. Thinly collimated sections (1 mm) are obtained for evaluating the circle of Willis. A 3- to 5-mm collimation is used for evaluating abdominal aortic aneurysms. The speed of the table can be increased (table pitch) to cover more anatomic area, such as the entire abdominal aorta and iliac bifurcation.

Intravenous contrast medium is administered at rates of 3 to 5 ml per second for a total of 90 to 150 ml, depending on the anatomic area to be imaged. Less contrast is needed for evaluating the neck vessels than for the abdomen. A minitest bolus of 10 to 20 ml is routinely used for abdominal studies to time the peak arterial opacification. The patient hyperventilates and is coached to produce a full inspiration. In general, a 30-second period is used for acquiring data. Most patients tolerate this procedure remarkably well, and the entire examination time is less than 15 minutes. Because of the need, in many cases, to hand edit and to subtract the spine and overlying bony structures, editing of the data set may take 1 to 1½ hours per case.

Preliminary comparisons with conventional angiography have shown that three-dimensional spiral CT angiography is an accurate technique. A retrospective study of patients referred for aortograms for renal artery stenosis was done when both maximum intensity projections have a 92% sensitivity for hemodynamically substantial stenoses. Computed tomographic angiography may prove to be a valuable adjunct in selected cases for the evaluation of postoperative grafts and in patients with metallic vascular stents and endoprostheses.

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Alerts, Notices, and Case Reports

Mollaret's Meningitis

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RECURRENT BENIGN ENDOTHELIOLEUKOCYTIC aseptic meningitis was first described by Mollaret in 1944 when he reported the cases of three patients. The European literature added additional cases, but reports of this disease did not appear in the English-language medical literature until 1972.[1] It remains a rare disorder (about 50 cases reported so far) of unknown cause that is usually mild and self-limited. This case is being reported because of the atypical presentation with confusion, aphasia, and fever without meningeal signs in an elderly patient.

Report of a Case

The patient, an 86-year-old woman with hypertension, in February 1988 had malaise, nausea, fever, and headache for five days. Two months later an episode of fever, confusion, and expressive aphasia recurred and cleared within 48 hours. The patient was seen after all symptoms had cleared from the second episode. A physical examination, computed tomographic (CT) brain scan, and an electroencephalogram (EEG) were unrevealing.

The patient was first admitted to a hospital in June 1988 for recurrent fever, nausea, and vomiting. She was disoriented, combative, and had confused speech. Headaches and nuchal rigidity were absent, and the results of a neurologic examination, with the exception of the confusion, were normal. She had a 2/6 systolic ejection murmur that was unchanged from previous examinations. The neurologic symptoms cleared completely within 24 hours, and her mentation returned to normal. A CT brain scan with a contrast medium and an EEG were again normal, as was a chest x-ray film. An electrocardiogram showed nonspecific ST abnormalities and left atrial enlargement. A carotid ultrasonogram showed mild plaquing of the left internal carotid artery. An echocardiogram showed no vegetations, intracardiac clot, or tumor. There were no notable abnormalities of the serum electrolytes, chemistry screen, or a complete blood count, although there was a mild persistent anemia due to chronic disease thought to be related to arthritis. Two blood cultures elicited no growth after seven days. The patient was discharged with a diagnosis of a probable hypertensive cardiovascular accident.

She was admitted a second time in mid-August 1988 when fever (as high as 39.2°C [102.5°F]), nausea, vomiting, disorientation, combativeness, and transient aphasia again developed. Again she did not have nuchal rigidity or headache. A neurologic examination revealed only mild expressive aphasia, and the general physical findings on admission were unchanged from those of her previous admission. The blood pressure on admission was 198/102 mm of mercury. After blood specimens were obtained for culture, a regimen of cefazolin sodium was started, and within 24 hours, all neurologic findings and fever cleared completely, with the blood pressure returning to normal.

The results of the following tests were normal or unchanged: a urine drug screen, abdominal CT scan, pelvic CT scan, EEG, two-dimensional echocardiogram, chest x-ray film, cranial CT scan with and without contrast, sinus x-ray films, ultrasonogram of the gallbladder, complement levels, serum electrolytes, chemistry screen, complete blood count, creatine kinase level, total protein content, serum albumin level, urinalysis, a Westergren sedimentation rate (25 mm per hour; normal, 10 to 30), and direct and indirect Coombs' tests. A gallium scan showed increased uptake in the left hip joint suggesting osteoarthritis (confirmed with plain films). The antinuclear antibody test was weakly positive at 1:40. One of six blood cultures grew *Staphylococcus epidermidis* thought to be a contaminant, and a urine culture grew 5,000 colonies of *Enterococcus faecalis*. The patient was discharged improved with a diagnosis of toxic encephalitis.

In October 1988 the patient was admitted a third time when she felt "chilled" and had nausea and vomiting. She was seen in the emergency department and had a temperature of 39.2°C (102.6°F) with a blood pressure of 220/120 mm of mercury; blood specimens were obtained for culture. The blood pressure subsequently dropped to 166/74 mm of mercury. The patient had no other symptoms at this time and was mentally clear. The results of general medical and neurologic examinations were normal, and she was admitted for observation. Her temperature rose to 40°C (104°F), and the patient rapidly became lethargic, then confused, with expressive and receptive aphasia developing. Despite the absence of nuchal rigidity, a lumbar puncture was done with the return of cloudy spinal fluid. A regimen of ampicillin, vancomycin hydrochloride, and gentamicin sulfate was started intravenously. All neurologic symptoms cleared completely within 36 hours, and she became afebrile within 48 hours. Antibiotics were continued for a total of 14 days and then stopped. Table 1 shows the results of CSF glucose and protein values, including a microscopic examination that showed inflammatory cell changes. A second lumbar tap eight days later showed clearing of the inflammatory changes in the CSF. A radionuclide cisternogram of the brain did not show CSF leaks, and during this hospital stay the results of the following tests were normal or unchanged: complete blood count, electrocardiogram, chest x-ray film, two-dimensional echocardiogram, routine blood chemistries, Westergren sedimentation rate, complement levels, urinalysis, febrile agglutinins, cryptococ-

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomographic
EEG = electroencephalogram

cal antigen, antinuclear antibody, and blood and CSF cultures. A thorough examination of her ears, nose, and throat revealed no evidence of a chronic or acute infection and no periodontal disease. She was discharged with a diagnosis of meningitis, probably bacterial.

Although clinically well, on November 30, 1988, the patient had another lumbar puncture (see Table 1). All CSF cultures were negative.

The final readmission was in September 1989, when she again presented with a fever of 39.4°C (103°F), a rapid onset of confusion and disorientation, and neck pain. Her physical findings remained unchanged except for her altered mental state. A pelvic examination revealed no disorder. Her symptoms cleared completely within 36 hours, and she remained clinically well for the duration of the hospital stay. Another lumbar puncture was done (Table 1). Results of the following tests remained normal or unchanged: complete blood count, routine chemistries, all blood and CSF cultures, stool guaiac, two-dimensional echocardiography, chest x-ray film, CT brain scan, antinuclear antibody, Lyme antibody, and antibodies to St Louis encephalitis, eastern equine encephalomyelitis, western equine encephalomyelitis, La Crosse encephalitis, and dengue encephalitis. Although the patient had no history of oral or genital herpes, herpes simplex virus antibody testing by enzyme immunoassay showed the herpes simplex virus type 1 antibody level to be high at 1.23 enzyme units (normal less than 0.22) and the antibody to herpes simplex virus type 2 elevated in the midrange at 0.46 enzyme units (normal less than 0.20).* A seven-day course of intravenous acyclovir sodium and ceftizoxime sodium was started, and she was discharged with the diagnosis of Mollaret's meningitis. The patient has remained well as of September 1993 without any further recurrences.

*Tests for the herpes simplex virus antibody were done by the American Medical Laboratories, Chantilly, Virginia.

Discussion

The essential features of Mollaret's meningitis are recurrent brief episodes of meningitis that alternate with symptom-free intervals. The attacks of meningitis occur suddenly, with the initial presentation being clinically indistinguishable from other forms of life-threatening meningitis. The symptoms reach maximum intensity within a few hours. They consist of headache, neck and back pain, nausea, vomiting, myalgias, arthralgias, and neck stiffness that persist for as long as three days.[1-4] During the attacks, Kernig's and Brudzinski's signs of meningismus are usually present. In their absence, the recurrent symptoms of nausea, vomiting, fever, confusion, combativeness, and aphasia seen in this patient did not prompt a lumbar puncture until the third hospital admission.

Temperatures as high as 40°C (104°F) occur during the episodes. As exemplified by this case, all signs and symptoms disappear as rapidly as they develop, and the patient is completely well until the next episode. The individual episodes vary in their intensity; occasionally two episodes can merge,[1] but the rule is long intervals at the onset and toward the later stages of the disease. After a number of years, during which a patient has recurrent episodes of a similar nature, the illness ceases as abruptly as it started. Usually patients have fewer than ten attacks. The patient's general health is not adversely affected, and neurologic residual abnormalities or sequelae are not seen.

Routine blood studies give varying results, with leukocytosis, leukopenia, and eosinophilia having all been seen. Circulating levels of immunoglobulin M may be elevated as well.[1,5] Increased erythrocyte sedimentation rates have also been documented. Examination of the CSF is the single most important study to do, with results showing a typical mild CSF protein elevation with an increase in the immunoglobulin (IgG and IgM) fractions, normal or elevated opening pressure, and rare depression of the CSF glucose levels.[3,5-9] Other characteristic spinal fluid changes seen in the first 24 hours include pleocytosis (almost always < 3,000 × 10^6 per liter [3,000 per mm^3]),[10] with a predominance of polymorphonuclear neutrophils and a large type of cell that has been called "endothelial" (Mollaret's cells). These mononuclear cells—one study has identified these cells as monocytic by

TABLE 1.—*Cerebrospinal Fluid Test Results in a Patient With Recurrent Mollaret's Meningitis*

Chemistry Level and Cell Content	*Date of Lumbar Puncture*			
	10/2/88	*10/10/88*	*11/30/88*	*9/2/89*
Glucose, mmol/liter (mg/dl)	3.8 (68)	3.1 (55)	3.7 (66)	3.7 (67)
Protein, grams/liter (mg/dl)	1.38 (138)	0.60 (60)	0.49 (49)	1.05 (105)
Cells/High-Power Field				
Leukocytes, × 10^6/liter (/mm^3)*	2,000	5	3	38
Differential cell count, fraction of 1 (%)				
Segmented neutrophils	0.60 (60)	0.24 (24)	1.00 (100)	0.97 (97)
Lymphocytes	0.01 (1)	0.76 (76)		0.03 (3)
Monocytes	0.39 (39)			
Erythrocytes, × 10^6/liter (/mm^3)*	6,000	14	1	3

*The numbers for both Système International units and conventional units are the same.

immunocytologic studies[11]—are characterized by the irregular, vague outline of their nuclear and cytoplasmic membranes and by their tendency to undergo rapid lysis while being examined in the counting chamber. Many of these cells appear only as "ghosts," and they are rarely seen after the first few hours of an attack. Although supportive of the diagnosis of Mollaret's meningitis, Mollaret cells are not pathognomonic of the disease, and their importance is unclear. After the first 24 hours, the CSF polymorphonuclear neutrophils disappear, and the pleocytosis becomes predominantly lymphocytic. There is also a rapid disappearance of the lymphocytic elements, and within a matter of days after an episode, the pleocytosis has disappeared or only a few residual lymphocytes may be present.

Cases of Mollaret's meningitis are equally divided between the sexes, with the age range being between 5 and 83 years. The duration of illness ranges from 1 to 11 years, although one case spanned 28 years.[6] The episodes of meningitis last from two to seven days, although in some patients an episode occasionally requires several weeks to resolve completely. Transient neurologic abnormalities may occur in as many as half of the patients during episodes of meningitis, and these include grand mal seizures, hallucinations, coma, diplopia, facial nerve paralysis, anisocoria, vertigo, syncope, speech impairment, and Babinski reflexes[1-4,6,7,10,12-17] These neurologic abnormalities should prompt a search for other disease processes.[3,6]

The cause remains an enigma. Causes of sterile recurrent lymphocytic meningitis from which Mollaret's meningitis must be differentiated include formes frustes of other diseases such as the Vogt-Koyanagi syndrome, Harada's syndrome, and Behçet's disease, or an allergic mechanism, lupus erythematosis, viral meningitis, familial Mediterranean fever, intraspinal tumors, fungal infections, intracranial epidermoid tumor, glioblastoma, Whipple's disease, intracranial hydatid cysts, or sarcoidosis.[1-3,5,14,16,18-21] The most difficult to differentiate from Mollaret's meningitis is the aseptic recurrent meningitis caused by epidermoid tumors.[16,20] Here the difficulty arises because the cyst ruptures and the contents, which become difficult to find, contain cell debris and ghost cells identical to those seen in the CSF of patients with Mollaret's meningitis. In the case reported here, the patient having remained free of further attacks for four years suggests the absence of an epidermoid tumor. No detectable involvement of other organ systems is seen in Mollaret's meningitis. In particular, mucous membrane ulcerations, dermatologic abnormalities, and ocular involvement are absent.

Associated viral infection is often suspected but seldom confirmed. Viruses that have been associated with Mollaret's meningitis include the Epstein-Barr virus, Coxsackie viruses B5 and B2, echoviruses 9 and 7, and herpes simplex virus types 1 and 2.[6,9,14,15,18,19,22-24] Increased circulating levels of natural killer cells in a peripheral blood smear[22] create circumstantial and speculative evidence that a virus is involved in the cause of this intriguing disorder. Other immunologic studies of the CSF reveal changes in the helper:suppressor ratio that are similar to those of other infectious diseases of the central nervous system.[11] Unfortunately, in the case reported, no viral cultures of the CSF were done and the relationship of the herpes antibodies to the clinical course can only be speculated.

To date, no form of treatment, including various forms of antibiotics, antihistamines, colchicine, estrogen, phenylbutazone, acyclovir, and steroids, has produced a definite influence on the course of illness in patients with Mollaret's meningitis.[1,6,8,9,12,13,20,23,25] Although no conclusions can be drawn by the case reported here, it is intriguing that the repetitive cycles of Mollaret's meningitis ceased after a short course of acyclovir infusion.

Conclusion

Mollaret's meningitis is a rare, poorly understood disorder whose cause remains obscure and the diagnosis made by exclusion. The course of the disease—albeit protracted in some patients—is benign and, unlike other forms of meningitis, does not pose a threat to the patient. Although the several hospital admissions may not have been prevented in this patient, earlier recognition of this disorder may have prevented the repeated extensive diagnostic investigations.

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Lymphocytic Hypophysitis

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LYMPHOCYTIC HYPOPHYSITIS is an unusual disorder that nearly exclusively affects women; fewer than 50 cases have been reported in the literature. The present case also is unusual because a normal computed tomographic (CT) scan had been obtained of the sella shortly before the development of a large pituitary mass due to lymphocytic hypophysitis. Lymphocytes were characterized using immunoperoxidase stains. A probably unrelated malabsorption syndrome later complicated her hormone replacement therapy.

Report of a Case

The patient, a 30-year-old woman who was a registered nurse and had four children, was troubled by depression and was treated with imipramine hydrochloride. Because of frequent migraine headaches, a CT scan of the head was done in July 1989 and was normal. The normal pituitary gland was well visualized.

In September 1990, she gave birth to her fifth child. She attempted to breast-feed but had little milk, and her menses did not return. She had worsened diffuse headaches and "poor vision" when tested for her driver's license in October 1990. That same month an ophthalmologist documented 20/20 acuity in her right eye, perception of hand motion only in the left eye, normal ocular findings, and bitemporal superior quadrantanopia. Magnetic resonance imaging of the brain revealed a large mass involving the sella and suprasellar region that measured 2 cm in transverse diameter in the suprasellar area. There was lateral displacement of the carotid arteries and elevation of the optic chiasm, but no invasion of the cavernous sinuses or Meckel's cavity. There were no cystic changes. There was prominent enhancement with gadopentetate dimeglumine (Magnevist) (Figure 1).

In October 1990, the patient was admitted for a transsphenoidal operation. She was a one-pack-per-day smoker and had just completed treatment with ciprofloxacin hydrochloride for a left lower lobe pneumonia. She did not use alcohol. Her weight was 70.5 kg (155.5 lb), temperature 36.8°C (98.2°F), pulse 84 beats per minute and regular, and blood pressure 102/68 mm of mercury. Pupils were equal and reactive. Visual field examination by confrontation revealed a pronounced decrease in her bitemporal fields. Visual acuity was 20/100 in the left eye and 20/40 in the right eye. The complete blood count, platelet count, prothrombin time, sedimentation rate, and serum sodium, potassium, glucose, and creatinine levels were normal.

A partial pituitary resection revealed lymphocytic hypophysitis. The soft pituitary fragments were white-tan in color, and frozen section showed an intense lymphoid infiltrate. The softness of the specimen possibly reflected an active inflammatory process. Microscopic sections showed small clusters of pituitary cells surrounded by inflammatory infiltrate and fibrous tissue (Figure 2). No epithelial tumor was identified. The inflammatory infiltrate was predominantly mononuclear cells and comprised mature lymphocytes, mature plasma cells, macrophages, and many eosinophils. No granulomas were present, and acid-fast and methenamine-silver stains failed to show organisms.

Immunoperoxidase stains were done using the frozen tissue. There was a mixture of T cells ($CD3^+$), B cells ($CD22^+$), and macrophages ($CD11e^+$), with $CD3^+$ cells predominating. B cells were arranged in nodules. Both κ- and λ-light chains were present. All of these findings were typical of a mixed inflammatory cell infiltrate. A placental alkaline phosphatase level was normal, and an S-100 test showed occasional dendritic macrophages.

After the operation transient diabetes insipidus developed. Her visual fields and acuity returned to near normal. She was discharged on a regimen of cortisone acetate, 25 mg each morning and 12.5 mg each evening. Magnetic resonance imaging of the brain performed in December 1990 showed apparent total resection of the pituitary tumor. She noted diffuse myalgias and gradually lost weight, from 72.6 kg (160 lb) in November 1990 to 65 kg (144 lb) in June 1991, 55.8 kg (123 lb) in December 1991, 49.4 kg (109 lb) in June 1992, and 47 kg (104 lb) in November 1992. She weighed 44.9 kg (99 lb) in May 1993, had a serum cortisol level of less than 28 nmol per liter (1 μg per dl) despite excellent compliance, and was referred by her primary physician to the Endocrine Clinic at East Carolina University School of Medicine, Greenville, North Carolina.

At that time she had no vision problems, occasional migraine headaches, and no galactorrhea. She was fatigued, mildly nauseated, and had diffuse joint aches, especially in her hands. She had no recent menses and

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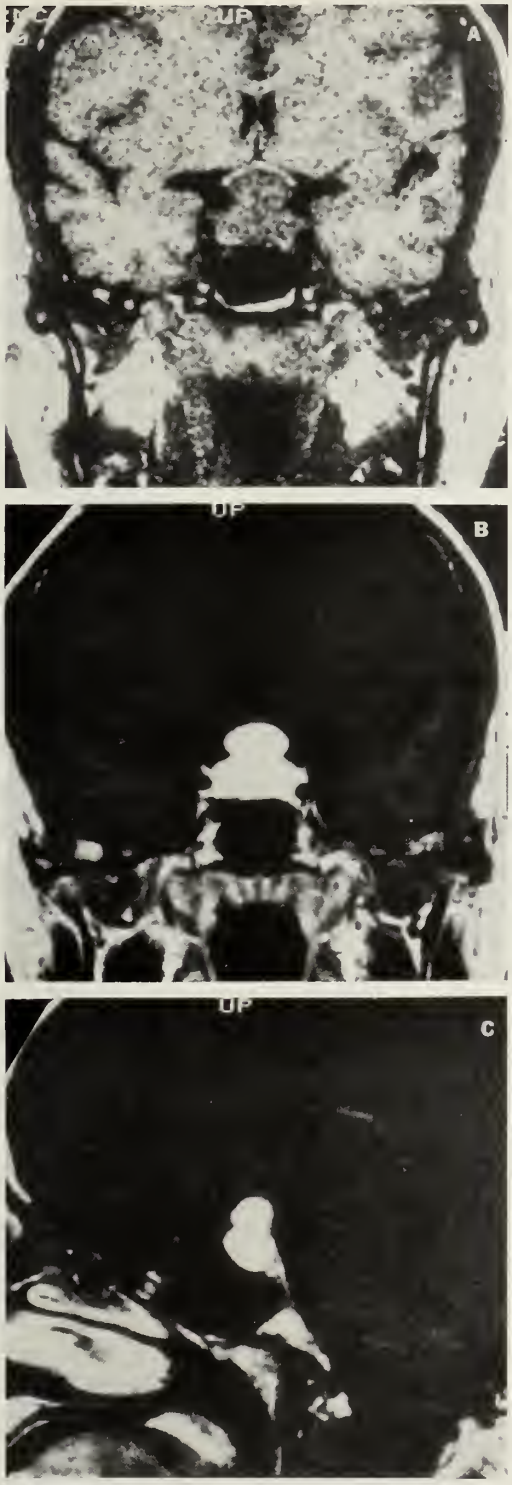

Figure 1.—T1-weighted magnetic resonance imaging of the head of a patient with lymphocytic hypophysitis 1 month postpartum. (**A**), A coronal view without contrast shows an hourglass-shaped pituitary mass with suprasellar extension compressing the optic chiasm. (**B**), A coronal view after the administration of 14 ml of gadopentetate dimeglumine (Magnevist) shows pronounced enhancement of the tumor. (**C**), A sagittal view after Magnevist was administered shows tumor enhancement.

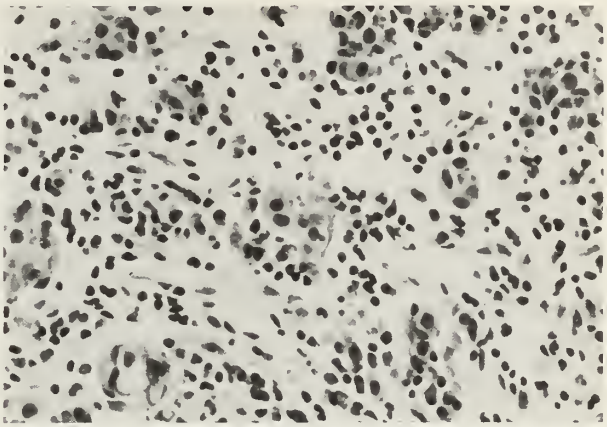

Figure 2.—Histologic section of the pituitary gland shows a small cluster of anterior pituicytes and a heavy inflammatory infiltrate of lymphocytes, plasma cells, and macrophages (hematoxylin and eosin stain, original magnification × 400).

described several episodes of "hot flashes." She reported that she first noted having diarrhea in November 1990. The stools were greasy, and the diarrhea was greatly worsened by eating fatty foods. Her blood pressure was 80/58 mm of mercury, pulse 72 per minute and regular, and respiratory rate 18 per minute. Her fundi and visual fields were normal. The hematocrit was 0.35 (35.2%), the mean cellular volume was normal, vitamin B_{12} and folate levels were normal, and the leukocyte count was 7.1×10^9 per liter (7,100 per mm^3). The prolactin level was 510 pmol per liter (12 ng per ml), luteinizing hormone 11 IU per liter, and follicle-stimulating hormone 18 IU per liter. The thyroxine level was 126 nmol per liter (9.8 μg per dl), and the thyroid-stimulating hormone level was 2.5 mU per liter.

A diagnosis of fatty stools with concomitant malabsorption of cortisone acetate was suspected. Her fatigue, arthralgias, and nausea resolved within three days after the cortisone acetate dose was increased to 50 mg every morning and 25 mg every evening. A 24-hour specimen for fecal fat was not successfully collected. A D-xylose test and the results of a small bowel biopsy were normal. Antiendomysial antibody was not detectable. An empiric trial of pancreatic enzyme replacement (pancrelipase [Creon capsules, Solvay Pharmaceuticals]) markedly decreased the diarrhea, she rapidly gained weight and improved clinically, and she has returned to work. On days that she forgets to take the pancreatic enzyme replacement, severe greasy diarrhea returns. There is no evidence of autoimmune disease and no significant family history.

Discussion

Lymphocytic hypophysitis is a rare inflammatory disease of the pituitary gland that may produce headaches, visual field abnormalities, and hypopituitarism. Fewer than 50 cases have been reported. It more commonly affects women during pregnancy or shortly after childbirth.[1-5] Only four cases have been reported in men.[6]

The cause is uncertain, and proposed possibilities include an autoimmune reaction[7] or an inflammatory re-

sponse after a viral infection.[8] It is seldom diagnosed preoperatively, and histologic examination is required to make a definitive diagnosis. When the diagnosis was suspected preoperatively in a case of a 29-year-old pregnant woman, a trial of dexamethasone was not effective, and a pituitary operation was required.[9] A different young woman, however, had visual field defects resolve during high-dose steroid treatment, and the field defects returned when that therapy was stopped.[10] In the patient in the present case, normal CT imaging of the sella predated the appearance of the tumor, the only such incidence ever reported, to our knowledge, for lymphocytic hypophysitis.

The natural history of lymphocytic hypophysitis remains poorly understood. Pituitary deficiencies have resolved in some patients, including adrenocorticotropin, or corticotropin, deficiency.[11-13] Although our patient continued to take her medication, she was unintentionally withdrawn from oral cortisone acetate therapy because of malabsorption of the drug, which resulted in clinical hypoadrenalism. This fortuitous circumstance provided insight into the potential of the pituitary gland to recover after the dual insults of hypophysitis and surgical intervention. The symptoms of hypoadrenalism persisted for nearly two years, suggesting that her corticotropin deficiency never recovered. The pituitary-thyroid axis remained intact. The malabsorption syndrome was completely corrected by pancreatic enzyme replacement, but returned on several occasions when the patient forgot to take the enzyme supplement. The precise reason for the pancreatic insufficiency remains uncertain.

A rapid onset of headaches and visual field abnormalities in a pregnant or recently pregnant woman should suggest the possibility of lymphocytic hypophysitis.

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Special Series

Health Effects and Prevalence of Vegetarianism

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Highlights

- Vegetarians tend to have lower weight, total serum cholesterol levels, and blood pressures than omnivores.
- Vegetarians have lower mortality than the population at large, attributable primarily to lower death rates from ischemic heart disease and certain cancers.
- Clinical nutritional deficiencies are uncommon even among strict vegetarians, although obtaining essential nutrients requires planning and, in some cases, vitamin supplementation.
- At present, vegetarians appear to make up less than 2% of the population, but substantial public health and environmental benefits would likely result from a more widespread adoption of vegetarianism.

Physicians often evaluate and recommend changes in the diet of their patients. Just as the role of dietary saturated fat in coronary artery disease led physicians to recommend moderation in red meat consumption,[1] the data on the physiologic effects of vegetarianism should encourage further reductions in meat consumption.* At the end of this article is a "Page for Patients" that refutes some of the common myths about vegetarianism.

Definition of Vegetarianism

Most epidemiologic and clinical studies of vegetarians classify them as either vegans, lactovegetarians, or lacto-ovovegetarians. Vegans eat no food of animal origin (except perhaps honey), and lactovegetarians eat dairy products. Lacto-ovovegetarians eat both dairy products and eggs and outnumber vegans in most reports. Because the elimination or reduction of alcohol, tobacco, and caffeine intake often accompanies vegetarianism,[2-6] many studies control for this.

Macronutrient and Micronutrient Composition of Vegetarian Diets

Vegetarians consume less total food energy (calories) than do omnivores because their diets are composed of less total fat and protein (but more total complex carbohydrate).[7,8] Vegetarians' diets are also comparatively low in cholesterol and saturated fat, have a higher ratio of polyunsaturated to saturated fats,[4,7,9] and have more fiber.[4,8]

The traditional concern about vegetarians' diets has been the adequacy of protein intake, especially of the eight essential amino acids. Data indicate, however, that vegetarians typically receive adequate protein.[2,7,9] The American Dietetic Association finds that "vegetarian diets usually meet or exceed requirements for protein" but recommends the consumption of a variety of high-protein plant foods such as grains, nuts, seeds, and legumes each day to obtain enough of each essential amino acid.[2] Eating enough food to meet energy requirements provides adequate protein for pregnant and lactating women as well.[2] In *Diet for a Small Planet,* Frances Moore Lappé provides an example of the way in which protein requirements can be met with a vegan diet.[10(pp160-167)] With a breakfast that included 1 cup of cooked oatmeal (5.4 grams of protein) and 0.5 ounces of sunflower seeds (3.5 grams), a lunch that included 2 tablespoons of peanut butter (7.8 grams) and 2 slices of whole wheat bread (4.8 grams), a dinner that included 1 cup of cooked beans (15.6 grams), 1 cup of cooked brown rice (3.8 grams), and 1.3 cups of broccoli (6.2 grams), with assorted other minor protein food sources (including mushrooms, carrots, apples, raisins, fruit juice, honey, and oil totaling an additional 7.9 protein grams), a total of 57.7 grams of protein and 1,993 calories would be consumed; the recommended dietary allowance for a woman weighing 58 kg (128 lb) consuming a 2,000-calorie diet would be 44 grams of protein. As more calories are consumed, more grams of protein are proportionately consumed. Lacto-ovovegetarians have additional protein sources: a cup of milk has 9 grams of protein, an ounce of cheese has 5 to 8 grams, and a medium-sized egg has 6 grams of protein.

The vitamin and mineral states of vegetarians have been studied by analyzing both food intake and plasma micronutrient levels. Vegetarians have adequate or better intake for most vitamins, including A, C, E, thiamine, and riboflavin.[7,9] Pyridoxine (vitamin B_6) intake has been found to be low, but one study found this true for omnivores as well, and the ratio of pyridoxine to protein intake—a physiologically appropriate correction, given the

*See also the editorial by S. Havala, MS, RD, LDN, "Vegetarian Diets—Clearing the Air," on pages 483-484 of this issue.

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ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
LDL = low-density lipoprotein

function of vitamin B_6 in amino acid metabolism—was adequate among vegetarians.[9] Tissue folate levels appear normal,[11] and one study found that vegetarians have a higher plasma α-tocopherol (vitamin E)-to-cholesterol ratio than omnivores,[12] which may contribute to their lower risk of atherosclerosis (as discussed later).

Although vegetarians have adequate intake and levels of many vitamins, they tend to have lower vitamin B_{12} and D intake and plasma levels than do omnivores. This is not surprising, as both these vitamins occur primarily in animal-derived foods (particularly fortified dairy products in the case of vitamin D). Although some plant-derived foods, such as seaweed or fermented soy products, have been considered valuable vitamin B_{12} sources, they are inadequate because their cobalamins are primarily inactive vitamin B_{12} analogues.[13] Physicians should be aware that the use of alcohol, tobacco, and certain drugs such as neomycin, colchicine, and aminosalicylic acid may contribute to vitamin B_{12} deficiency by causing B_{12} malabsorption in both omnivores and vegetarians.[14]

In a study of 44 elderly Dutch vegetarians, most of whom ate dairy products and eggs, 6 men (35%) and 13 women (13%) had vitamin B_{12} levels below normal,[9] as did 15 of 93 (16%) younger Australian vegetarians.[11] Of the omnivore controls in each study, 2 of the Dutch (5%) and none of the Australians had low levels. The Australian group reported no clinical findings related to vitamin B_{12} deficiency, and the Dutch subjects were called "apparently healthy." The subnormal vitamin B_{12} levels found in the older group were thought to be due to the 5- to 20-year lag between vitamin B_{12} deprivation and depletion and to the relationship between older age and atrophic gastritis.[14] A 1981 review found that diet alone was seldom implicated in published reports of clinically significant vitamin B_{12} deficiency in vegetarians (with malabsorption due to gastrointestinal disease being a particularly frequent cofactor).[14] Vitamin D plasma levels in a group of mixed but primarily lacto-ovovegetarians (n = 37) were less than 20 mmol per liter in 14 (38%), indicating inadequate stores; this was also true for 19 of 69 omnivores (28%).[7] Although people may vary in their ability to extract available vitamin B_{12} from dietary sources, all vegans presumably require vitamin B_{12} and, especially among children, vitamin D supplementation. Lacto-ovovegetarians, particularly those using vitamin D-fortified milk, may not necessarily require vitamin B_{12} or D supplementation.[2]

Studies have found mineral intake adequate in vegetarians, with the possible exceptions of iron and zinc. Typically cited "best" sources of these minerals include meat and, for zinc, seafood. Grains and legumes also contain substantial amounts of iron and zinc, and green leafy vegetables contain iron[15]; hence, the consumption of adequate plant protein should provide adequate iron and zinc.[16] Intake studies have had various results, from no difference between vegetarians and omnivores[17] to considerably inadequate zinc and iron intake in a small number of vegetarian women.[16,18] Even when intake seems adequate, however, some investigators have found lower plasma ferritin and zinc levels in vegetarians than in omnivores.[9,11] The explanation probably lies in the poorer bioavailability of plant-derived iron, along with an increased intake of fiber and phytates by vegetarians,[2] as phytates (inositol esters of hexaphosphate found in whole grains) and fiber bind iron and zinc. Ascorbic acid, when consumed simultaneously with iron, enhances iron absorption, and for this reason eating foods high in vitamin C has been recommended to vegetarians.[2] Overall, the serum zinc and iron status of vegetarians is typically normal on a population basis, but a small segment of young women vegetarians may be at risk for deficiency because of their preferences for a diet of primarily fruits and vegetables, eschewing grains and legumes.[18] Some evidence exists that vegetarians may accommodate to their diet by increasing the absorption of these minerals despite their high dietary fiber and phytate intake.[15] Those nonnutritive dietary constituents also decrease calcium absorption, deficiency of which can occur in vegans, although essentially never without simultaneous vitamin D deficiency.[19]

Regarding both micronutrient and macronutrient intake, vegetarian diets in third world nations may be different and are more likely to be associated with nutrient deficiencies.[19] Our review includes primarily studies of adult vegetarians in industrialized nations.

Effects on Disease Risk Factors

As adduced in the previous section, vegetarians in industrialized nations can readily, and usually do, obtain adequate nutrition, and clinically notable deficiencies rarely appear. Despite lower ferritin levels, anemia does not occur more frequently in this group,[20] and the low ferritin levels may offer certain advantages, as will be discussed. Vegans assume some specific risks that can be avoided entirely by awareness and dietary planning, and, as a group, they appear to enjoy many health benefits.

One benefit with many ramifications is vegetarians' consistently lower weight compared with omnivores,[3-5,7,9,21] possibly a consequence of their reduced total energy consumption, although increased exercise may also play a role in this often health-conscious group.[2] Various investigators have found lower blood pressures among vegetarians of many cultures,[4] but numerous confounding variables exist, such as lower weight and differences in alcohol, caffeine, and sodium intake. One group in Australia controlled for some of these factors by comparing Seventh-Day Adventists with Mormons. Seventh-Day Adventists are frequently lacto-ovovegetarian and have been extensively studied, and Mormons provide a nonvegetarian control group because they, like Seventh-Day Adventists, avoid using alcohol, tobacco, or caffeine. The Australian researchers found, after adjusting for weight, height, and age, that the omnivorous Mormons had higher blood pressures (6 to 8 mm of mercury systolic, 3 to 5 mm of mercury diastolic) and a greater prevalence of

mild hypertension (2% versus 10%, respectively; defined as >140/90 mm of mercury) than did the vegetarian Adventists.[4]

The cause of this lower blood pressure is not entirely certain. Vegetarians do not appear to have lower sodium intake as measured by urinary excretion,[4,5] but two studies found substantially higher potassium excretion than in omnivores.[4,5] The authors of one study speculated that increased potassium intake causes decreased peripheral resistance through a variety of mechanisms.[5] Direct potassium supplementation, however, as well as other manipulations designed to provide specific pseudovegetarian interventions, have had no effect in normotensive subjects.[22,23] A randomized crossover trial demonstrated that a complete lacto-ovovegetarian diet, however, can lead to a small but significant decrement of the systolic blood pressure (5 mm of mercury) in mildly hypertensive omnivores.[24]

The lower intakes of cholesterol and saturated fat with a greater proportion of total monounsaturated and polyunsaturated fats clearly affect the serum lipid profile of vegetarians. Plasma total and low-density lipoprotein (LDL)-cholesterol levels are consistently lower than in control omnivores[3,12,20,21,25] and compared with mean United States values.[8] An analysis of nine studies comparing vegans or unspecified vegetarians with omnivores reported the average serum cholesterol levels of the three dietary groups as 4.1, 4.7, and 5.0 mmol per liter (158, 182, and 193 mg per dl), respectively; LDL values were 2.1, 2.6, and 3.1 mmol per liter (81, 100, and 120 mg per dl), respectively.[8] Plasma triglyceride levels do not differ consistently among these groups, however.[8,20,25] The effect on high-density lipoprotein (HDL)-cholesterol levels is also inconsistent: compared with omnivores, higher[21] and lower[25] levels have been reported; one review found no consistent trend for a difference in HDL cholesterol in nine studies comparing vegetarians and controls.[8] This is not surprising in a population that has both lower weight (usually increasing HDL-cholesterol levels) and lower total fat intake (sometimes decreasing HDL-cholesterol levels). The difference in the ratio of total to HDL cholesterol seems to be the same[25] or lower[20,21] in vegetarians compared with controls; the review found a trend toward a lower ratio in vegetarians, but no true meta-analysis was done.[8]

Dietary fibers—especially soluble fibers such as guar gum, pectin, and oat gum—have been shown to lower total cholesterol levels, primarily by lowering LDL-cholesterol and triglyceride levels, without consistent effects on HDL-cholesterol levels.[26-29] Because vegetarians (especially vegans) may have fiber intakes two to three times those of omnivores,[29] fiber intake may contribute to vegetarians' favorable lipid profiles. Higher fiber intake may also help reduce risks of other diseases such as bowel cancers, gallstones, and diabetes.[29]

Two interesting studies of the metabolic effects of dietary lipids involved feeding a lacto-ovovegetarian diet to nonvegetarians with crossover control to an omnivorous diet.[30,31] The vegetarian diets resulted in lower total and LDL-cholesterol levels, but no change in total HDL levels. Another study compared plasma lipids of dedicated vegans with those of lactovegetarians, finding greater than 20% higher total and LDL-cholesterol levels and 7% higher HDL-cholesterol levels in the lactovegetarians.[32] The authors concluded that fatty dairy products affect LDL cholesterol more than HDL cholesterol. Even if HDL-cholesterol levels decline with a vegetarian diet, it appears that the greater decline in LDL cholesterol more than compensates for any deleterious effect.

The protective mechanism of vegetarianism on cancer remains uncertain. Secondary bile acids, formed by the action of intestinal bacteria on primary bile acids, are implicated in tumor growth. A study of fecal bile acids in vegetarians and omnivores found that the secondary:primary ratio increased with increasing meat consumption and that omnivores (presumably because of their relatively low dietary fiber content) had a third the stool bulk of vegetarians, resulting in omnivores having a higher total fecal bile acid concentration.[37] Many epidemiologic studies have found strong negative correlations between fiber intake and carcinoma of the colon, breast, and prostate.[38] In addition to the effects of omnivores' low fiber intakes, their higher dietary fat and cholesterol intakes have also been epidemiologically linked to colon and breast cancer.[19]

There may be other, less obvious health risks associated with animal tissue consumption. For instance, although the health effects are uncertain on a population basis, organisms higher in the food chain tend to concentrate heavy metals and other organic and inorganic toxins in their tissues.

Morbidity and Mortality in Vegetarians

The largest prospective study of vegetarians comprised 27,530 Seventh-Day Adventists in California who were observed for 21 years beginning in 1960. A lower mortality occurred among the Adventists as a group compared with controls.[33] Inasmuch as only 54% of Seventh-Day Adventists are vegetarian, 99% do not smoke, 90% do not drink alcohol, and 41% avoid caffeine,[6,34] isolating the effect of diet is essential. The investigators achieved this by using dietary information obtained from a questionnaire administered at the beginning of the study. They found that, even within the population of Adventists, an increasing frequency of meat or poultry consumption correlated positively with rising all-cause mortality, even after adjusting for tobacco use, and that an increasing frequency of green salad consumption correlated negatively with mortality.[34] Another analysis found that death rates from colorectal cancer—which cancer, along with lung cancer, the Adventists seem most protected from—and coronary heart disease among this group decreased as the consumption of eggs or meat decreased.[35] In addition, they found, particularly for men, that those who had become vegetarians at an earlier age were at a lower risk for coronary heart disease mortality. Similarly, in comparing nonsmoking Adventists and control men, coronary disease mortality was significantly lower in the Adventists, even though only half were vegetarian.[6]

A British study helps confirm the protective effect of a vegetarian diet on the heart—and allays concerns that Adventists' protection is a genetic, rather than a lifestyle-related phenomenon. Male and female British vegetarians and omnivores, both of whom frequented health-food stores—and were therefore thought to be "health conscious"—were observed prospectively, and the vegetarians had only 42.8% of the deaths expected from ischemic heart disease versus 60.1% among controls ($P < .01$).[3] Introducing a vegetarian diet even after the diagnosis of coronary artery disease may have benefit. Ornish and colleagues took patients with angiographically documented lesions and randomly allocated them to either their usual diet and standard care or to a vegetarian diet (with egg whites and nonfat dairy products allowed) and stress management, smoking cessation treatment, and a moderate exercise regimen.[36] At the end of a year, total and LDL-cholesterol levels had fallen (24.3% for total cholesterol levels and 37.4% for LDL-cholesterol levels; $P < .02$ for the difference between the intervention and usual-care groups' cholesterol improvements), HDL-cholesterol levels decreased slightly, although not significantly, in both groups, and there were higher rates of regression of coronary artery lesions and lower rates of progression among intervention patients on follow-up angiography.

Studies have also found that vegetarian diets may reduce the risk of cancer mortality. When Seventh-Day Adventists are compared with socioeconomic-status-matched non-Adventists, they have lower death rates for colon carcinoma and, among postmenopausal women, breast carcinoma.[6,29,39,40] Analyses within Adventist populations, though, have been more ambiguous: although a case-control study of Seventh-Day Adventists with colon cancer found that patients were significantly more likely to have eaten meat in the past than were controls (matched for age, sex, race, and religion),[39] an analysis of cancer mortality among 20,000 Adventists found no significant correlation between meat consumption and colon, breast, and prostate carcinomas.[40]

In addition to ischemic heart disease and cancer, other diseases that seem to have lower prevalence in vegetarians include type II diabetes mellitus, gallstones,[41] and osteoporosis.[42,43] Among Adventists, diabetes contributed to mortality 45% as often as expected compared with all US white adults.[44] With adjustment for age and weight, meat consumption correlated positively with diabetes-related mortality in men and with self-reported diagnoses of diabetes in both men and women.[44] Vegetarians' lower risk for type II diabetes is biologically plausible. Obesity and fat and protein intake correlate positively with type II diabetes,[45] and vegetarians have lower rates of these risk factors. High fiber intake lowers postprandial glucose levels in normal and diabetic subjects and has been postulated as the principal factor protecting hunter-gatherer and subsistence-agricultural societies from type II diabetes.[46,47]

On the origin of vegetarians' lower morbidity, a critical question remains: Is it in their decreased consumption of meat or their increased consumption of vegetables and fruits? Probably both factors contribute and perhaps synergistically. A decreased intake of total calories, total fats, cholesterol, saturated fat, and iron, a higher proportion of polyunsaturated versus saturated fats, and an increased intake of fiber and antioxidant vitamins (C, E, and vitamin A-related compounds) could all favorably influence health. For instance, peroxidation of LDL cholesterol is likely an important pathogenic event in atherosclerosis, and this process occurs under conditions of low antioxidant availability and high free-ionic-iron availability.[48] A recently published study of Finnish men demonstrated a positive correlation between the risk of myocardial infarction and high serum ferritin concentrations and found that, of the various foods examined, the consumption of meat had the strongest correlation with serum ferritin levels.[49] Vegetarians, as discussed earlier, tend to have lower serum ferritin levels and a higher α-tocopherol-to-cholesterol ratio than omnivores, theoretically offering double protection from lipid peroxidation.

Prevalence of Vegetarianism

While we have cited many studies examining the physiologic effects of vegetarianism, few have studied its prevalence. We therefore endeavored to examine the prevalence of vegetarianism by surveying four cities in central California. These data come from the Stanford Five City Project, a communitywide health education intervention and community organization program targeting the primary cardiovascular risk factors. For the purposes of this article, the major methodologic features of the Five City Project included five cross-sectional, household-based surveys conducted in four communities in California between 1979 and 1990. The survey groups were primarily white (non-Hispanic) and were of varied educational levels. The main conclusions,[50] the design and methods of the project,[51] and many of the items used in this article[52] have been published previously.

For this analysis, we examined the responses of participants aged 20 to 74 years to the question, "For how many entire days during the last week did you eat strictly vegetarian foods? In other words, for how many days did you not eat any of the following foods: meat, poultry, fish, egg yolks, or cheese (other than low-fat cheeses like ricotta or low-fat cottage cheese)?" To examine the association between the number of days per week of only vegetarian meals and various physiologic and demographic outcome measures, we performed Spearman correlations and derived P values to determine significance.*

We found that vegetarians were rare in the population, and there was no change in prevalence during the 1980s ($P > .25$ for a logistic regression with a y variable of >0 vegetarian days per week) (Table 1). Those with more vegetarian days in the previous week were significantly ($P < .05$) more likely to be younger, female, more educated, and of higher household income. Those with more vegetarian days had lower weight, plasma cholesterol levels, systolic and diastolic blood pressures, and lower (better) Framingham risk scores. Regarding their health and dietary habits, they had higher health knowledge scores,

*Darius Jatulis and Helena Kraemer, PhD, provided statistical consultations.

TABLE 1.—*Prevalence, Characteristics, and Health-Related Habits of Vegetarians and Omnivores in the Stanford Five-City Project*

	Number of Vegetarian Days/Week						
Variable	*0 Days*	*1-3 Days*	*4-6 Days*	*7 Days*	*SD*	*r*	*P Value**
Prevalence rates, %							
1979-1980 (n = 2,045)	76.5	16.8	3.5	3.2			
1984-1985 (n = 2,076)	81.7	14.8	3.0	0.4			
1989-1990 (n = 2,092)	77.9	16.9	4.2	1.0			
Total sample size, 1979-1990	4,887	1,004	220	97			
Demographic comparisons							
Mean age, yr	41.1	38.7	39.4	41.6	14-16	.05	.0001
Sex, female, %	52.3	57.2	66.8	60.8		−.06	.0001
Mean education, yr	13.4	13.8	13.7	13.8	3-4	.05	.0001
Mean income, $	30,610	27,284	27,475	27,556	22,000-26,000	−.08	.0001
Physiologic comparisons, mean							
Body-mass index, kg/m^2	25.5	25.0	25.0	23.9	4-5	−.05	.0001
Cholesterol level, mg/dl†	192.3	187.8	187.4	189.1	42-45	−.05	.0002
Pulse rate, beats/min	70.8	70.9	69.9	69.8	11-12	.00	.9
Systolic BP, mm of mercury	122.7	121.4	120.2	122.1	15-17	−.03	.02
Diastolic BP, mm of mercury	75.1	74.5	74.6	74.3	10-13	−.02	.1
Framingham risk score	3.6	3.0	3.2	3.2	3-5	−.05	.0001
Dietary and other health habit comparisons							
Health knowledge‡	7.6	8.0	8.7	7.6	3-4	.05	.0001
Smokers, %	25.5	23.5	20.6	27.1		−.02	.2
Mean kcal/kg/day expended	37.9	38.4	37.0	38.8	5-10	.06	.0001
Mean kcal/day	2,171	2,079	1,863	2,075	833-1,135	−.07	.0001
Mean fat calories, %	36.4	34.5	34.2	35.7	9-12	−.08	.0001
Morbidity comparisons§							
Physician visits	4.2	4.2	5.8	4.4	7-16	.01	.6
Sick days	9.7	8.8	14.0	6.8	27-51	.02	.1
Days in hospital	7.8	7.4	8.4	3.1	3-13	−.05	.3

BP = blood pressure, SD = standard deviation

**P* value based on a Spearman correlation coefficient.
†To convert conventional units (mg/dl) to Système International units (mmol/liter), multiply by 0.2586.
‡Maximum possible score is 17.
§Mean number in previous year.

exercised more, and consumed fewer calories and less fatty food. There were no significant correlations between vegetarianism and morbidity as measured by sick days, clinic, or hospital visits.

There are several limitations to this study. The first is our definition of vegetarianism. We, in fact, preferentially identified both vegans and lactovegetarians who ate heart-healthy (low saturated fat, low cholesterol) dairy products. Those who frequently ate eggs or whole-milk cheese would not have been able to answer "7 days" to our study question, and this may have contributed to the low prevalence of vegetarianism. In addition, we do not know the nature of the foods actually consumed or how typical the subjects' diets were during that preceding week. Regarding the data's generalizability, some might claim that residents of the towns in central California where cardiovascular disease intervention and control are practiced have an unusually high prevalence of vegetarianism compared with residents of other regions in the United States. A 1980 study of 605 Massachusetts physicians and lawyers, however, found that 1.5% called themselves vegetarian (although this population is also atypical).[53]

Although this study begins to answer some of the previously unaddressed questions about vegetarianism, there remain other important unresolved questions. For example, what effect would the isolated elimination of red meat—and the continued consumption of fish, poultry, or both—have on risk factors and morbidity? Several studies have suggested that high fish consumption may reduce the risk of heart disease, and this finding has been incorporated into many dietary recommendations for Americans.[1] Similarly, if we are correct that vegetarians benefit from the high antioxidant levels in many fruits and vegetables, to what extent could these positive health effects be achieved by antioxidant supplementation of an omnivorous diet? Although the balance of evidence suggests that vegetarian diets produce lower disease risks, less morbidity, and lower mortality than omnivorous diets, we still have much to learn about the source of that decreased risk.

Conclusion—Vegetarian Lifestyle

Beyond both the documented and the anecdotal health advantages, people choose vegetarianism for a number of other reasons: economic, ethical, and ecologic. Meat is costly in both pecuniary and planetary terms; it has been estimated that the production of 0.4 kg (1 lb) of American beef requires 7 kg (16 lb) of grain and soy[10(pp69-71)] and the

equivalent of 3.8 liters (1 gal) of gasoline for agricultural petrochemicals, transportation, and processing.[54(p225)] Bypassing livestock feeding makes more food energy and protein available at lower cost, using fewer resources.

Many consider vegetarianism a matter of individual taste, an ethical choice, a political statement, or even a personal quirk. Yet, the balance of the data suggests that vegetarianism likely improves individual as well as societal health. Although many vegetarians lead ecosensitive lifestyles, personal politics need not be altered to derive health benefits from vegetarianism. Our review of the data suggests that people, particularly those at high risk for cardiovascular disease and cancer, should be encouraged to consume increasingly vegetarian diets.

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Are Vegetarians Healthier?

A Page for Patients From THE WESTERN JOURNAL OF MEDICINE and Your Physician

Myth: *Being a vegetarian is fine for people who live on communes, but what good would it do me?*

Reality: There are actually lots of ways vegetarianism could improve your life: you're likely to live longer, be healthier, and be kinder to your pocketbook and to the planet.

Myth: *If I were a vegetarian, would I have the strength to live a long, healthy life?*

Reality: Some studies have found that vegetarians may be as little as half as likely to die in a given year as are nonvegetarians. This is mainly due to their lower rates of heart disease and cancer, especially cancer of the large intestine. While some of this difference may be due to other parts of vegetarians' lifestyles—for example, having lower rates of smoking cigarettes or drinking alcohol—much of it seems to be the result of their diet.

Myth: *How can I get enough protein if I don't eat meat?*

Reality: The American Dietetic Association finds that "vegetarian diets usually meet or exceed requirements for protein." Some vegetarians (called lacto-ovovegetarians) get some of their protein from eggs and dairy products. Some vegetarians do not eat dairy products or eggs; this group, called "vegans," probably has the best health of all, with the lowest blood pressures and cholesterol levels. Clearly, high-protein plant foods (like grains and beans) can provide all the protein you need.

Myth: *What about vitamins and minerals?*

Reality: Vegetarians who eat enough calories and who eat a wide variety of nonanimal foods may actually end up better off in the vitamin and mineral department than are nonvegetarians. A major vitamin advantage vegetarians have is their higher intake of vitamins called antioxidants. These vitamins (such as A, C, and E) occur naturally in many fruits and vegetables and have been shown to protect against heart disease and cancer. While vegans may need extra vitamins D and B_{12}, medical problems from vitamin deficiencies are rare, even in this group. Your physician or a nutritionist can give you more information about this issue.

Myth: *Isn't it expensive, complicated, and boring to be a vegetarian?*

Reality: Expensive? Anyone who's been to the grocery store lately can tell you that a pound of beans is a lot cheaper than a pound of beef. Complicated? Check out a couple of cookbooks, and you will see how easy it is to prepare tasty, interesting food. We recommend *Diet for a Small Planet* and *Recipes for a Small Planet* (both by Frances Moore Lappé, Ballantine Books), *The New Laurel's Kitchen* (Ten Speed Press), and *Sundays at Moosewood Restaurant* (Simon & Schuster). Boring? How many different types of animals do you usually eat? Maybe ten? Compare that with the dozens of different kinds of fruits and vegetables in any produce department, and you'll get a sense of the variety available to vegetarians.

Myth: *What difference does it make to anyone else what I eat? A pound of food is a pound of food, whether it's soybeans or beef.*

Reality: The production of 1 lb (0.45 kg) of American beef requires 16 lb (7.25 kg) of grain and soy. Eating the grain and soy yourself saves oil (used in transportation and farm chemicals), land, topsoil, and money. The evidence is strong that reducing meat production would be a major advantage for the global environment. (For more information on this, read Jeremy Rifkin's *Beyond Beef*, Dutton Books.) One other person who cares about your diet is your physician—that's why this page is in the waiting room. Why don't you ask your physician about whether eating less meat would be healthier for you?

History of Medicine

19th-Century Academic Examinations for Physicians in the United States Army Medical Department

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During the latter half of the 19th century, the United States Army commissioned medical officers or hired civilian physicians to serve its troops. The civilian physician signed a contract for services, and the candidate for a commission was subjected to rigorous examinations before becoming an officer. The rigorous testing of prospective medical officers was necessary because of the lack of standardization in the education of physicians. Examples of the test, statistics, and individual records show how the Army dealt with unqualified candidates.

(Sohn AP: 19th-century academic examinations for physicians in the United States Army Medical Department. West J Med 1994; 160:472-474)

In the 19th century the United States Army was inconsistent in its evaluation of prospective physicians who sought a position in its hospitals. For example, rigorous physical and difficult academic examinations were required before a physician became a commissioned officer. In contrast, some civilian physicians who had questionable credentials obtained contracts and became "contract" army surgeons. This dilemma is highlighted by the commissioned and civilian surgeons whose various tours of duty took them to Nevada military hospitals during the frontier era, 1860 to 1890.

The decade of 1860 ushered in the Civil War and an exponential growth of Native American-settler conflicts throughout the American West, which led to an acute shortage of military doctors.[1(p215)] In 1861 there were only 64 commissioned medical officers in the United States Army. In 1865 Congress, during demobilization, temporarily prohibited the commissioning of medical officers. As a result, in the early 1870s the number of contract civilian physicians known as acting assistant surgeons increased and eventually equaled the number of commissioned physicians titled assistant surgeons.[2] This action prevented even those candidates who had passed the required Army examination from obtaining a commission. As early as 1848, the Army Examining Board in New York City could not pass enough medical officer candidates to fill ten vacant positions. Later in 1848, only 7 of 21 physicians in Philadelphia passed the required examination. This trend continued for 20 years.[1(pp198-199)] Some failed because they had physical disabilities or were not citizens, but most of the high failure rate was the result of poorly educated candidates.

During the mid-19th century, the quality of medical education in the United States was completely unregulated. One method of obtaining medical training was to pay $100 a year for an apprenticeship with a practicing physician. A student could take didactic courses consisting of two repetitive four-month courses. Elias Samuel Cooper, MD, started a school in San Francisco, the first medical school in California—which eventually became Stanford. Hubert H. Toland in 1864 started Toland Medical College, which became the University of California, San Francisco, Medical College—that required two 18-week terms.[3] Established in 1858, Cooper Medical College had a prerequisite of either a one-year apprenticeship under a respected physician or high school training. This was unusual as many medical schools did not have minimal entrance requirements, such as proficiency in reading and writing or mental and physical fitness examinations.[4]

Medical licensing was also virtually nonexistent before the Civil War. When Jacksonian philosophy, or Republicanism, swept the country, "freedom of choice" became more important than protecting the public from unscrupulous and quack medical practitioners. Because many states did not require a medical license, anyone could hang out a shingle and treat patients. It was said,[5(pp354-355)]

> In no country in the world is quackery carried on to so enormous an extent as it is in the United States. . . . [T]hus it is no uncommon thing to find a person calling himself a Doctor in New York [who] . . . up to the very day that he left for "the land of liberty," had been . . . a shoe maker, tailor or liquor dealer.

Confronting the problem, the Army established strict academic examinations for medical officer candidates. About the examination, one candidate recalled,[6(p199)]

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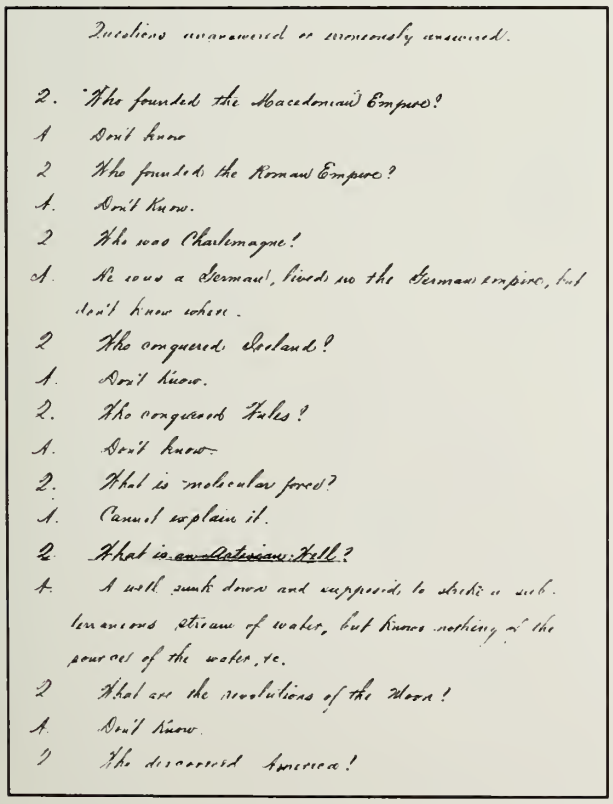
The worse [sic] part of it was the very long oral examination on Saturday for it covered not only medicine and surgery, but a large number of outside subjects as tests of general education—languages, history, geography, mathematics, literature, geology, botany, and many other subjects.

By looking at some of the examinations and reading comments about them, the educational background of physician candidates and the knowledge of medicine in the late 19th century are suggested. First, the Army invited a person to take the examination, usually after the candidate had expressed interest. Next, the board required three letters of recommendation that included statements from acquaintances about the candidate's education, training, and moral character. Apparently letters from universities were not required because none are found in the medical personnel files of 68 early Nevada physicians. A letter from an acquaintance simply stated that the candidate "graduated from Yale with honors," but included no documentation. The last step, the test, usually lasted three days. The board tested the candidates' general knowledge in addition to medical knowledge.

In 1874 Conant Bowdoin Brierly, stationed at Fort Halleck, Nevada, took the examination and failed. Brierly, who graduated from Toland Medical College, failed so completely that the Army, in an unusual action, terminated his contract (Figures 1 and 2).[7] Brierly did not know that Alexander the Great founded the Macedonian Empire; that, according to legend, Romulus and Remus founded the Roman Empire; that Charlemagne was King of the Franks and the first Germanic ruler of the Romans; that the Vikings, Normans, and Henry VIII of England conquered Ireland; and that the Romans conquered Wales. He did not know that an artesian well is a well in which the water rises above the level of the water in the ground, or that it takes the moon 29½ days to make one revolution around the earth. He also did not know who discovered America.


Questions unanswered or imperfectly answered.

2. Who founded the Macedonian Empire?
A. Don't know
2. Who founded the Roman Empire?
A. Don't Know.
2. Who was Charlemagne?
A. He was a German, lived in the German empire, but don't know when.
2. Who conquered Ireland?
A. Don't know.
2. Who conquered Wales?
A. Don't know.
2. What is molecular force?
A. Cannot explain it.
2. What is ~~an artesian well~~?
A. A well sunk down and supposed to strike a subterraneous stream of water, but knows nothing of the sources of the water, &c.
2. What are the revolutions of the Moon?
A. Don't know.
2. Who discovered America?

Figure 1.—Samples of the preliminary and oral examination of Dr C. B. Brierly, United States Army Surgeon, are shown (from National Archives[7]).

The following are examples of medical-related questions that Brierly failed to answer correctly or at all:

- How are the short bones divided? *Answer:* "I don't know."
- What muscles are attached to the coccyx? *Answer:* "I don't know."
- What muscles are attached to the lesser trochanter? *Answer:* "I don't know."
- Pathology: *Examiner's comment:* "Knew nothing of pathology."
- Practice of medicine: [Had heard of digitalis, but said it was a sedative used for rheumatism and fevers.] *Examiner's comment:* "Of disease of heart and lungs he knew nothing."
- Obstetrics: *Examiner's comment:* Gave a very general and vague description of the mechanism of labor, with many inaccuracies."
- Toxicology: *Examiner's comment:* "Very limited knowledge of subject."
- What is the composition of blood? *Answer:* "I cannot give it."

The five tests I reviewed demonstrated a lack of uniformity because different examining boards in different parts of the country wrote the tests. Devising a uniform academic test may have been impossible given the distances and the state of communication in the 1800s.

Even graduates of better-known eastern schools had trouble with the examination. George Martin Kober, a graduate of Georgetown Medical College, Washington, DC, who was stationed at Alcatraz in San Francisco, California, and later at Fort McDermit, Nevada, in 1874, took the test and failed.[8] After he appeared before the medical board, a friend advised him to retake it, but there is no indication he did so. He became Dean of Georgetown Medical School from 1901 to 1928 and was a leader in hygiene and medical education. Another easterner, Abel F. Mechem, a graduate of the University of Maryland, Baltimore, who served at Fort Churchill, Nevada, took the examination in 1867 and failed. He was advised to take it again in six months, and he then passed.[9]

The Army's Medical Department was sometimes so desperate to commission qualified men that the rules were bent. For example, although regulations stipulated that candidates be between 21 and 28 years of age, the Army waived the requirement for 36-year-old Charles Winne, a graduate of Jefferson Medical College, Philadelphia, Pennsylvania. He passed the test in 1874 and served in the army for 28 years.[10]

When a sufficient number of commissioned officers was not available, the military hired civilian doctors known as contract surgeons. Some of the contract sur-

Figure 2.—Dr William H. Arthur drew a cartoon of his examination for admission to the Medical Department of the United States Army (from Hume[6]).

geons requested examination by the Army board. A military commission assured a physician a career with advancement and a pension whereas a contract surgeon received no pension and little advancement. In Nevada during the period of this study, 45 of the 68 physicians (66%) were on contract and not commissioned. Some contract surgeons were substandard but nevertheless got contracts. Scrutiny continued, and the Army annulled contracts when the person performed poorly, as was the case with Siegesmund Kisffy. Kisffy, the first civilian surgeon at Camp McGarry, Nevada, had a diploma from the University of Pesth, Hungary, a certificate from the Eastern Medical Board of Examination of New Orleans, and another from the Harvard Association of New Orleans. He signed a contract on August 18, 1866, but the Army annulled his contract six months later because he was "totally deficient in medical qualifications."[11]

This brief description of the examination of physicians in the 19th century demonstrates the difficulties the US Army had in selecting its medical doctors.[12-14] The fact that medicine was not a cohesive profession and that medical training was not uniform compounded the problem. By the 20th century when accredited schools developed uniform training and were able to produce quality physicians, the Army eliminated rigid academic examinations. During World War II, it was no longer necessary to test a physician's academic knowledge before issuing a commission in the military.

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Commentary

Preventing Bone Disease Requires Diligent Management in Patients With Renal Failure

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When we received the letter to the editor by F. I. Polsky, MD, and M. A. Fullmer, MD, elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE, *we felt it deserved a commentary. Felix Kolb, MD, has had extensive experience managing patients with complex clinical problems before and after renal transplantation.*

LINDA HAWES CLEVER, MD
Editor

The miseries of a young woman with end-stage renal disease—refractory anemia, hypertension, prolonged hemodialysis after the rejection of three renal allografts, autonomous hyperparathyroidism leading to total parathyroidectomy, the "hungry bone" syndrome, and finally, probably permanent hypoparathyroidism—described by F. I. Polsky, MD, and M. A. Fullmer, MD,[1] are reminiscent of an old motion picture serial entitled "The Perils of Pauline." The heroine encounters a series of mishaps from which she is rescued just in the brink of time.

This case report deserves comment because patients with similar complications are seen with increasing frequency in large dialysis and transplantation centers as the lives of patients with end-stage renal failure are prolonged for many years. Some of these complications (autonomous secondary hyperparathyroidism, severe renal osteitis) can be anticipated and possibly averted; others (calcinosis, aluminum bone disease) that are in part iatrogenic could be ameliorated by careful management of the patient's parathyroid function and phosphate balance.

A brief review of the genesis of these complications and their proper management seems in order.[2-4] The kidney is an active endocrine organ handling phosphate and calcium excretion and the synthesis of the active form of vitamin D, 1,25-dihydroxyvitamin D3 (calcitriol) largely under the control of parathyroid hormone. With decreasing creatinine clearance (<0.67 ml per second [40 ml per minute]), phosphate excretion is diminished, leading to a subtle fall in ionized calcium and to parathyroid stimulation, which in turn normalizes serum phosphorus and calcium levels.

At this stage, a reasonable restriction in dietary phosphate and adequate calcium and vitamin D intake will reestablish homeostasis. As renal function declines further, phosphate retention becomes more severe, with impaired production of calcitriol and further parathyroid hyperplasia. Intermittent dialysis is now initiated. The use of aluminum-containing phosphate-binding agents in moderate doses and large amounts of either calcium carbonate or calcium acetate (calcium citrate is contraindicated because it enhances aluminum absorption)[5,6] and the addition of the active vitamin D compounds 25-hydroxycholecalciferol (calcifediol) or calcitriol will again return the serum calcium and phosphorus levels to normal and avert the development of secondary osteitis fibrosa cystica. It is imperative to monitor the serum parathyroid hormone level regularly, using the generally available immunoradiometric assay (IRMA). If the level exceeds two to three times the upper limits of normal (>16 pmol per liter [160 pg per ml]), bone disease will occur. An admixture of osteitis and osteomalacia is usually found with progressive elevations of the serum alkaline phosphatase level. The combination of osteitis, osteomalacia, and at times also osteosclerosis and osteoporosis has been called "renal osteodystrophy" with striking changes in skeletal x-ray films and scans. To suppress severe secondary hyperparathyroidism, intermittent intravenous calcitriol is now generally used.[7] The serum phosphorus level must be carefully controlled because exceeding the solubility product of the calcium level times the phosphorus level (>70) will lead to heterotopic calcification. There has been an increase in the incidences of both tumoral calcinosis and calciphylaxis in our patients and those at other dialysis centers, possibly related to the use of large doses of calcium carbonate and calcitriol.[8,9]

The distressing symptoms of severe pruritus, painful subcutaneous nodules with skin necrosis, and vascular calcification—which led to amputation of both legs in one of our patients—require drastic measures, including strict control of the serum phosphorus level, adjustment of the dialysate calcium, and frequently subtotal parathyroidectomy.[10]

If, despite serious attempts to control parathyroid hypersecretion, severe secondary autonomous parathyroid hyperplasia with progressive hypercalcemia (also called tertiary hyperparathyroidism) occurs, subtotal

(Kolb FO: Preventing bone disease requires diligent management in patients with renal failure. West J Med 1994; 160:475-477)

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parathyroidectomy is required. This happened in the case reported, in which the patient had recurrence of hyperparathyroidism in the remnant gland, leading to total parathyroidectomy. While recurrent hyperparathyroidism may be due in part to poor patient compliance with medical therapy, a recent report suggests that a chromosomal change occurs in large hyperplastic parathyroids, leading to adenoma formation.[11] Parathyroid size can now be monitored by ultrasonography,[12] and recurrent hyperfunctioning parathyroid glands can now be visualized by the use of the radionuclide technetium Tc 99m sestamibi.[13] Some centers do total rather than subtotal parathyroidectomies with transplantation of a portion of one of the smaller hyperplastic glands to the forearm to lessen the "hungry bone" syndrome and avoid permanent hypoparathyroidism.

Parathyroidectomy is contraindicated in patients who have the recently recognized syndrome of aluminum osteodystrophy,[14] with adynamic or "low-turnover" bone disease, associated with severe bone pain and fractures. It can be diagnosed only by proper bone biopsy with aluminum staining, which shows aluminum at the calcification front with osteomalacia and osteoporosis.

Aluminum osteodystrophy is unresponsive to vitamin D therapy, which may actually markedly aggravate the hypercalcemia. It could represent a state of relative hypoparathyroidism because aluminum suppresses parathyroid function. Parathyroid hormone levels are generally lower than in patients with osteitis fibrosa. The removal of aluminum by deferoxamine mesylate has been useful in some patients with this disorder, but is associated with serious side effects such as mucormycotic infections.[15] Avoiding aluminum-containing phosphate binders and substituting calcium and magnesium carbonate may help these patients.[16,17]

Other complications seen in patients on long-term dialysis are amyloidosis due to the retention of microglobulins with bone cyst formation and carpal tunnel syndrome.[18] Prolonged erythropoietin therapy can cause refractory hypertension and, rarely, massive bone marrow hyperplasia with the erosion of bone, which led to pathologic hip fracture in one of our patients (R. Garcia-Kennedy, F.O.K., unpublished data, 1990). The cause of the distressing myopathy and neuropathy seen in some patients is not known, but high levels of parathormone and aluminum may be contributory factors.

Before renal transplantation is undertaken, the parathyroid and bone status should be carefully evaluated to avoid disastrous complications, such as severe hypercalcemia. Severe hyperparathyroidism and florid bone disease must be partially controlled before transplantation. After a successful transplant, the "Perils of Pauline" are not over. A new set of problems related to the return of normal renal function and the need of immunosuppression to prevent rejection of the transplant arises.[19,20]

The use of high-dose corticosteroids changes the high-turnover bone state of secondary hyperparathyroidism to a low-turnover state by suppressing osteoblast function. This can be monitored by serial serum osteocalcin (γ-carboxyglutamic acid) measurements. Corticosteroids enhance the resorption of trabecular bone. The concurrent administration of cyclosporine will partially reverse this by increasing bone turnover, but this does not occur in an organized fashion, and in general, bone disease progresses in the first year after transplantation in patients receiving steroids plus cyclosporine. Azathioprine probably has an effect similar to corticosteroids.[21] Steroid-treated patients must receive adequate amounts of calcium and vitamin D to offset the antiabsorptive action of cortisone. This is often difficult because some patients show persistent hypercalcemia and hyperparathyroidism for several months after transplantation.

Hypophosphatemia may occur with the return of normal renal function and must be treated with phosphate supplementation. Patients on steroid therapy are also subject to infections such as osteomyelitis and to osteonecrosis of joints, especially of hips, knees, and shoulders.[21,22] The early recognition of this serious disorder by bone scan and magnetic resonance imaging may avert the need for joint replacement. Cyclosporine toxicity includes hypertension, hirsutism, and severe hyperuricemia and gout requiring allopurinol therapy. In the future, the availability of noncalcemic analogues of vitamin D, such as 22-oxacalcitriol, will make it possible to treat persistent hypercalcemia more rapidly, avoiding the need for parathyroidectomy.[23]

Post-transplantation osteopenia can be monitored readily with serial measurements of bone mineral density using dual-energy x-ray absorptiometry.[24] A reduction in corticosteroid use and the administration of sex steroids, calcitonin, and the newer bisphosphonates may be needed to reverse persistent or progressive post-transplantation osteopenia.[20]

This review illustrates the complex nature of the metabolic changes seen in patients with end-stage renal disease, both before and after renal transplantation. Careful control of the parathyroid hormone level and of the calcium-phosphate product by a judicious regulation of diet, dialysate, calcitriol dose, and the early recognition of possible hazards to patients similar to those in the case reported in this issue may lessen some of their miseries and improve the quality of their lives. In our medical center, the combined efforts of nephrologists, transplant physicians, and endocrinologists have averted or greatly reduced the severity of some of these perils.

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Commentary

'What Does the Law Say?'
Law, Ethics, and Medical Decision Making

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Physicians and medical students are seldom tempted to act boldly where legal issues are concerned. Instead, the growing legal presence in medicine has generated resentment and confusion among physicians[1] and infused an element of hesitancy and caution into both medical practice and medical training. The effects of malpractice fears on medical practice and the physician-patient relationship have been widely documented,[2,3] and observers at many medical schools have reported that medicolegal anxieties have compromised students' professional training.[4] Legal concerns have intruded into physicians' and medical students' consciousness in other ways as well. Never before have there been as many regulations, statutes, and precedents affecting such a broad range of a physician's professional life. From the "Baby Doe" regulations to court rulings on the end-stage of life, from the subtleties of informed consent requirements to the legal intricacies of treating patients with the acquired immunodeficiency syndrome, medical professionals face a nearly overwhelming barrage of medicolegal concerns.

Although legal questions are profoundly important, physicians face an increasing number of equally complex ethical challenges. The profession has responded. Medical journals regularly publish ethical discussions, and medical schools now require some manner of formal training in ethics. Often, however, the subject matter of legal and ethical debates overlaps, and when it does, the ethical discussion is frequently infected by the legal concerns. The most common and often the first question posed by physicians and medical students in ethical discussions is, "What does the law say?"

Legal and ethical conclusions on biomedical issues are occasionally identical, and legal rulings have in some instances accelerated the scrupulous consideration of ethical problems in medicine. In addition, accurate knowledge of the law is sometimes necessary so that physicians will feel free to treat their patients in a more ethical manner.[5] The confluence of legal and ethical is far from complete, however, and a great danger arises when the two are conflated. When an ethical dilemma is framed first and primarily in legal terms, it risks dramatically skewing the inquiry from the outset and may allow inappropriate considerations and assumptions to guide the discussion. Physicians' interest in the law for self-protection is understandable and legitimate, but the fear of liability may lead to an overreliance on legal conclusions and approaches to moral problems. Medical professionals must recognize the limited goals and insights of the law and legal thought. As a rule, legal standards are unreliable guides to ethical conduct and should never be allowed to substitute for, or dominate, ethical analysis.

Law as a discipline and a body of knowledge is far from useless in the weighing of ethical options in medicine. Law has proved an effective discipline in the formal, institutionalized resolution of conflicts. Legal reasoning and argumentation are based on a vigorous and open debate of the alternatives of a position. They are an especially useful means of revealing weakness in opposing positions. In addition, the law is frequently viewed as an illustrative collection of beliefs and attitudes, "a cultural artifact, a moral deposit of society."[6,p4] As such, legal conclusions on various biomedical issues might occasionally serve as rough reflections of ordinary moral reasoning.

Despite these plaudits, legal tradition, legal argumentation, and the legal system of judges, juries, and courts do not guarantee a morally or socially correct result. Law, after all, has been used to support slavery, involuntary sterilization, and discriminatory practices and successfully used to delay or thwart a large number of ethical, beneficial, and just civil rights and social welfare policies. Legal reasoning is frequently nothing more than the playing out of a relatively mechanical, recurring set of arguments and counterarguments.[7] The legal adversarial format and sometimes abstract legal principles are seldom the most appropriate means of effectively and sensitively resolving the complex ethical challenges routinely generated by modern health care.[8]

In the interest of objectivity and consistency, the legal process, training, doctrine, and tradition have tended to downplay humanity and individuality. In fact, the law demonstrates its ostensible impartiality by focusing the bulk of its attention on the principles involved and not on the person.[9] While this jurisprudential approach may be successful in achieving some limited goals, namely consistency, it does not lead inevitably to just results, and it is a clearly inappropriate model for resolving bioethical dilemmas. The medical relationship consists of flesh-and-blood physicians and patients. Principles and doctrines

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may inform ethical deliberations, but they should never dominate them. For example, legal-style reasoning tends to focus ethical discussions on the relative rights and duties of the physician and patient. To some extent, a concern with rights-based duties is appropriate. But a myopic concentration on rights and duties may suppress other equally or more important sources of responsibility and ethical guidance. Moral problems might also be fruitfully analyzed in light of personal loyalties and professional expectations and informed by cultural conventions and religious traditions.[10] A legally dominated discussion could undervalue these other elements that are clearly relevant to the resolution of ethical problems. Finally, the "numbing and suppressing of emotion," a sometimes unfortunate side effect of dispassionate legal analysis, may work to impair one's moral sense. Some writers, and, I suspect, much of society, believe that the application of both heart and mind, intuition and reason, are required in moral inquiries.[11]

In addition, it is reasonable to ask whether judges are well suited or well situated to make decisions of great ethical magnitude and complexity. Typically, judges' talents and training are appropriate for the duties assigned them. The best judges have excellent "legal minds." They are careful, critical, and lucid thinkers ideally equipped to make legal decisions. But their education and experience—ordinarily three years of law school and a stint in academe or private practice—do not necessarily supply them with the array of resources necessary to identify, unravel, and reconcile the complexities of medical ethical situations. The judge's role, though sometimes ill defined, is ultimately circumscribed and limited by the facts and issues raised by a particular case. A court's first duty is to resolve the specific dispute presented for adjudication. The court's ruling on that case sometimes generates doctrine that can be applied in analogous situations. It is important to remember that the development of that doctrine, although general in applicability, was spawned in part by the particular facts of the original dispute. Consequently, the character of cases presented to judges and courts for adjudication may undermine the universality and utility of the resulting legal doctrine.

By their nature, courts deal with medical relationships gone wrong. This raw material for medicolegal doctrine engenders a frame of reference and precedents that frequently misapprehend the nature of the medical relationship.[12,13] For example, several observers have recognized the unintentionally baneful effect of legal doctrine on the practice of informed consent. Because the law primarily emphasizes the importance of informing patients of the risks of procedures, typically less attention has been focused on other aspects of physician-patient communication that are equally important for patient autonomy and well-being.[12] The President's Commission for the Study of Ethical Problems in Medicine concluded that "its vision of the patient-professional relationship" cannot be achieved "primarily through reliance on the law."[13(p152)]

As the 19th century jurisprudential adage notes, "Hard cases make bad law." Virtually all central bioethical issues represent hard cases, and it is arguable that there are numerous instances of "bad law" in biomedical jurisprudence. Legal decisions and statutory proclamations are subject to the vicissitudes of interest group politics, the personal philosophy of judges and legislatures, idiosyncratic viewpoints, bad research, and poor briefing. Not only do legal rules and conclusions regularly deviate from well-reasoned ethical precepts on the same subject, but some scholars argue that law typically lags substantially behind morality.[14(p196)] Consequently, it is sometimes uncertain whether a legal doctrine will even serve as a reliable reflection of collective cultural wisdom, let alone as an objective, well-reasoned, comprehensive ethical principle.

Real clinical situations typically present a complicated blend of ethical and legal concerns that are often difficult to consider in isolation. A particular treatment option or course of action may be legal and ethical, legal and unethical, illegal and ethical, or illegal and unethical. In addition, some medical decisions may be legal and ethical but place the physician at an increased risk of civil liability.[15] A clinical decision based solely or predominantly on legal considerations may in some cases yield an ethical result. That result, however, is not preordained, and in other cases an overreliance on the legal perspective undermines careful, complete, and subtle ethical analysis.

Consider for example a discussion of the ethics of a forced cesarean section. The hypothetical patient, a young woman, is 36 weeks' pregnant, with an undersized pelvic structure and an oversized fetus. Her physicians are convinced that the child cannot be delivered vaginally without severe injury or death to infant, mother, or both. The mother, however, fears surgery and is committed to a "natural" delivery. Discussions frequently focus first on the legal aspects: "Can I get a court order to do a cesarean?" "If I get a court order, am I immune from liability?" "If I do not get a court order and the child is delivered vaginally but is injured or dead, can I be held liable?"[16,17]

These are important questions, but they largely miss and clearly distort the ethical component of the problem. Doing a court-sanctioned cesarean section may be legal, but unethical.[18] Honoring the woman's wishes and attempting a vaginal delivery may be legal and ethical, but could subject the physician to a risk of suit if the child is injured during delivery. Doing a cesarean section against the woman's will without a court order could be both illegal and unethical. In deciding the core ethical question—whether to operate against the woman's will, to risk the health of the fetus, or both—the legal questions confuse rather than aid the ethical reasoning process. As Mattingly has explained, we need ". . . to gain a fresh perspective on this issue by stepping back from the legal debate and considering in a systematic way how ethical guidelines for prenatal medical care are altered by transition to the two-patient obstetric model."[19(p14)] The initial relevant question for physicians in such cases should not be, "Can I get a court order, and will it protect me?" but rather, "Should I operate against the will of the patient?"[17]

Other scenarios raise similar questions. For example,

a group of physicians are treating an unconscious, 72-year-old man with long-term diabetes mellitus diagnosed with gangrene of the toes. The medical staff recommends amputation of the foot to improve the patient's condition and save his life. The patient's wife, a university professor, reports that her husband has explicitly told her that he would rather die than undergo an amputation, and she refuses to permit the operation. The hospital petitions the local court to sanction the operation. The court agrees with the physicians, and the amputation is performed. Although it is clear that the physicians who amputated the elderly patient's foot were acting legally and enjoyed a certain degree of legal protection, it is not as certain that they acted ethically in pursuing a court order to defy what appeared to be a patient's wishes reliably relayed by a close family representative.

How should physicians act in situations where legally correct practice is not necessarily synonymous with ethically correct practice? Should the law be bent or legal dangers ignored to provide better and more ethical medical care? It has been suggested that "[S]ometimes it may be necessary for the health care professional to violate the duty to obey the law in order to fulfill his responsibility to his patient."[20(pp214-215)] Conversely, are there instances in which what is otherwise the most ethically and clinically proper course of action can be legitimately influenced by certain legal considerations? For example, are some instances of defensive medical practice justifiable even though they are not otherwise indicated?

The answers to these questions will depend on the facts of the specific case and are best left to the clinical decision makers and their patients. Individual physicians will have to make personal decisions on how they will weigh and balance patients' needs, ethical duties, and legal requirements and risk. Whatever their decision, it is imperative that they do not mistake law for ethics, nor ethics for law. Physicians are entitled and required to know what the law says about relevant topics. But they must also be prepared to analyze the most profound issues facing their profession without being diverted by sometimes irrelevant legal questions.

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Editorials

Immunologic Glomerular Disease—New Prospects for Specific Therapy

One of the most vexing problems in contemporary clinical medicine remains our inability to specifically, or even effectively, treat most forms of immune-mediated glomerular disease. Remarkably, since the introduction of corticosteroids and immunosuppressive reagents nearly three decades ago, there have been few notable additions to the nephrologist's armamentarium. Given the fact that glomerular disease accounts for the majority of patients worldwide in whom end-stage renal failure develops, the societal and economic implications of this failure are of major importance. Given the cost and complexity of renal replacement therapies and the associated physiologic disturbances these incomplete modalities engender, progress towards the specific treatment of these disorders must remain a central, if not the primary, focus of nephrologic research. In this issue of the journal, William G. Couser, MD, has concisely summarized our current concepts of the pathogenesis of immune-mediated glomerular disease and the recent findings of his research group that may have direct implications for more specific and effective forms of treatment.[1]

Our current inability to deal with these disabling disorders should not be construed as the consequence of a lack of interest, as investigations into the pathogenesis of glomerular disease have a long and distinguished history in which several distinct phases may be discerned. In ancient times, physicians clearly recognized the association between proteinuria, the hallmark of glomerular injury, and kidney disease. As noted in *Aphorisms* (XXXIC), Hippocrates observed that

> [t]he urine is best when the sediment is white, smooth and consistent. Fatty substances floating on the surface are to be dreaded, for they are indications of melting. *When bubbles settle on the surface of the urine,* they indicate disease of the kidneys. [emphasis added]

The association between proteinuria and renal disease was extended by Rufos of Ephesus (100 AD), who published an extensive "Treatise on Diseases of the Kidney and of the Bladder." Patients with foamy urine—proteinuria—were noted to have sclerotic kidneys, little pain, and a tendency to have edema. The observation of this association has been generally ascribed to Richard Bright (1789-1858), who described kidneys as "having a hard and contracted state, which was connected with the secretion of an albuminous urine and was accompanied by repeated and obstinate anasarca."[2(p4)]

Scientific investigations into the pathologic mechanisms operative in glomerular injury may be dated to the beginnings of the current century. Schick noted the delay between streptococcal disease and the appearance of acute nephritis,[3] a finding attributable to the formation of immune complexes and subsequent complement consumption. The development of immune complex or complement-dependent models of glomerular disease in the 1950s to 1960s permitted the definitive delineation of the roles of antigen-antibody complexes, complement, and infiltrating inflammatory cells in these processes.[4-6] The widespread use of percutaneous renal biopsy, coupled with the introduction of immunofluorescent techniques, facilitated the application of basic research findings concerning complement and immune complexes to an improved categorization of human glomerular disease.

The ability to culture consistently individual glomerular cell types, beginning in the mid-1970s, led to a virtual explosion in the information available concerning the distinctive cellular biology of these cells. Perhaps most important was the gradual appreciation that intrinsic glomerular cells (endothelial, mesangial, and epithelial) play major roles in the evolution of the glomerular inflammatory process that are independent of infiltrating leukocytes. These studies, which now number in the hundreds, have delineated the determinants of cellular proliferation, the factors that control the metabolism of the extracellular matrix, the ability of glomerular cells to secrete multiple cytokines, and, finally, the cellular responses to inflammatory mediators released by infiltrating leukocytes and platelets.

The direct application of these voluminous and often conflicting in vitro observations to events taking place within the intact glomeruli of experimental models or during human disease represents the contemporary phase of research. For example, numerous studies have noted that cultured glomerular mesangial cells both secrete and respond to transforming growth factor β-1 (TGFβ-1) in a number of ways, including variable inhibition of growth rates, augmented synthesis of matrix proteins, and modulation of matrix-degrading enzyme synthesis. Recently, Border and colleagues have directly tested the importance of TGFβ-1 secretion in a model of immune complex-mediated glomerulonephritis characterized by a marked expansion in the mesangial matrix.[7] Remarkably, the inhibition of TGFβ-1 action with an infused neutralizing antibody inhibited glomerular matrix accumulation. In a similar manner, Floëge and co-workers have demonstrated a direct in vivo effect of infused platelet-derived growth factor (PDGF) or basic fibroblast growth factor on mesangial cell proliferation and matrix accumulation.[8]

The direct testing of the hypotheses generated by tissue culture studies for their possible relevance to the glomerular inflammatory process is an important step for the eventual development of specific anti-inflammatory strategies, including the targeted delivery of specific genetic constructs to individual glomerular cells. The intrinsic mesangial cell, which is centrally involved in nearly all forms of progressive glomerular disease, offers a particularly attractive target for specific transfection. Due to the absence of a limiting basement membrane, the mesangial cell is directly in contact with plasma components. Numerous studies have shown that particulate matter ranging in size from ferritin molecules to aggregated immunoglobulin appears in the mesangium within minutes

of injection, whereafter endocytosis rapidly occurs. These properties are ideal for the mesangial localization of specific vectors containing various genetic constructs. The feasibility of this approach was recently demonstrated whereby glomerulosclerosis was induced by the in vivo transfection of TGFβ-1.[9]

Based on these observations, the future of specific therapy for glomerular disease appears bright and will conceivably include a specific ribozyme or antisense-mediated reduction in prosclerotic cytokine synthesis—TGFβ-1, PDGF—as well as the introduction of defined anti-inflammatory genes. Attaining these goals may be expected to finally provide clinicians with effective means of treating these disabling disorders.

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Human Immunodeficiency Virus and the Peripheral Nerves

IN MANY WAYS what syphilis was to previous generations, the human immunodeficiency virus (HIV) infection is to today's generation—a highly prevalent chronic disease with frequent sexual transmission, affecting multiple bodily systems, and often producing devastating cerebral deterioration. One of the main differences in the neurologic morbidity caused by these two organisms has been the frequent occurrence of neuromuscular disease in patients with HIV infection—a rarity in syphilis. Elsewhere in this issue of the journal, Robert G. Miller, MD, an authority in the field, reviews the many peripheral nerve and muscle dysfunction syndromes produced by HIV infection.[1]

Exactly how rapidly infection with the HIV organism affects the peripheral nervous system is an unsettled issue. The Guillain-Barré syndrome has occurred shortly after infection with the virus. Patients at this stage may have minor systemic symptoms, and in such patients the spinal fluid usually shows pleocytosis. More relevant to the question of early affliction of the peripheral nervous system is the fact that nerve conduction studies of sural nerves in patients in the latent phase of HIV infection have shown abnormalities compared with controls.[2] Whether these asymptomatic patients with slowed nerve conductions are destined for later clinically substantial peripheral nerve dysfunction is another interesting and unresolved question. (This matter of the early involvement of the peripheral nervous system in HIV infection parallels that of the early involvement of the brain. There is no agreement as to whether neuropsychological impairment due to HIV infection occurs in seropositive persons who are asymptomatic).[3] The fact that a peripheral neuropathy may be the first clinical manifestation of HIV infection has important clinical implications, particularly for the protection of patients in electromyographic laboratories.

The mechanisms by which HIV infection can adversely affect peripheral nerves are, as Miller points out in his review of the syndromes, at least four in number:

- Actual infection of and damage to peripheral nerves by the HIV antigen,
- Damage resulting from an autoimmune process occurring in response to HIV infection,
- Concurrent infection of nerve or nerve root by cytomegalovirus, and
- Other adverse effects on peripheral nerve such as concurrent vitamin B_{12} deficiency.

All of the above are, of course, in addition to direct toxic effects on peripheral nerve resulting from the therapeutic agents directed to the virus itself.

In patients with distal sensory neuropathy, HIV has been cultured from biopsy specimens of peripheral nerve, and inflammatory lesions in such nerves have been described. It has been postulated that the pathogenesis of such neuropathy is tissue destruction mediated by infected T cells and macrophages. Others, however, have disputed the mechanism of direct HIV infection of peripheral nerve. Because the virus has also been cultured from spinal fluid and other tissues in patients who show no major signs of disease, its presence in tissue is not absolute proof of infection as a cause of clinical disease.

Autoimmune mechanisms are probably involved in at least some of the clinical neuropathy syndromes, such as demyelinating neuropathies and radiculopathies, both acute and chronic. These frequently occur in cases of hyperglobulinemia, and antiperipheral nerve antibodies have been found in these patients. They frequently respond to treatments commonly used for autoimmune neuropathies—plasmapheresis and prednisone.

How important cytomegalic inclusion virus (CMV) infection is in the pathogenesis of the various kinds of HIV-associated neuropathy is unclear. Miller discusses the fact that CMV antigen has been most consistently associated with the specific syndrome of polyradiculopathy; CMV inclusions have also been reported in a few cases of mononeuritis multiplex associated with inflammation and

axonal loss in peripheral nerves. In the late distal sensory neuropathy of HIV infection also, CMV infection in various organs has been reported along with the finding of CMV in the dorsal root ganglion of a single case.[4]

The exact role of vitamin deficiency and environmental toxins, particularly on the late distal sensory neuropathy of HIV infection, is unknown. There has been one report of a significant abnormality of vitamin B_{12} metabolism in patients with HIV infection and neuropathy.[5] It is, of course, distinctly possible that a subclinical neuropathy in HIV-infected patients becomes symptomatic when a patient is exposed to minor amounts of environmental toxins or minor degrees of deficiency that are harmless to healthy persons.

Many interesting theoretical and practical questions relevant to the dysfunction of the neuromuscular system in HIV infection remain to be resolved. What is the relationship of the early neuromuscular complications to the early effects of the virus on the immune system? These effects are activation of the immune system as evidenced by markers on T cells and increased serum levels of β_2-macroglobulin. High levels of these "activation markers" have been associated with an increased risk of what has been called "short-term progression" of clinical HIV disease. It would be of interest to know if there is also association with the development of one or more of the neuromuscular complications. Also of interest is the question whether infection by different strains of the HIV virus carry different risks to the central or peripheral nervous system and whether there is any relation to the other immunologic features of HIV infection, for example, hyperglobulinemia.

Finally, many questions remain as to the appropriate treatment of these neuromuscular syndromes. One of the most interesting is the question of the prevalence of CMV infection requiring treatment. The results of the treatment of polyradiculopathy with ganciclovir are in many patients, as pointed out by Miller and others, impressive.[6] Because CMV is so prevalent in HIV-infected persons and because the antigen has been found in peripheral nerves, should the treatment be tried in all patients with late peripheral nerve complications of HIV infection?

Because HIV antigen has been found in peripheral nerve in some of these patients, are there patients in whom the neuropathy might be reversed by treating the HIV infection? The answers to these questions may soon be forthcoming.

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Vegetarian Diets—Clearing the Air

A 1992 SURVEY conducted by the market research firm Yankelovich, Clancy, and Shulman and commissioned by *Vegetarian Times* magazine showed that almost 7% of the American public, or about 12.4 million people, consider themselves vegetarians. Previous estimates of the prevalence of vegetarianism in the United States gave a number closer to 4% of the population.

Closer inspection of the Yankelovich figure reveals that of the 7% of those surveyed who called themselves vegetarians, most of them actually ate meat sometimes, although they usually avoided red meat. A better term for these respondents might be "meat restricters." The majority cited health concerns as the reason for adopting a mostly vegetarian diet.

It is heartening to learn that at least a portion of the American public is motivated to assume an active role in managing its own health care by taking preventive measures, such as adopting a more plant-based diet. Given that vegetarian diets are associated with decreased mortality from most of the chronic, degenerative diseases and conditions that afflict westerners,[1] this trend toward a healthier diet should be supported and encouraged by health care professionals, particularly the primary care physicians with whom patients place the most trust in guiding their health care decisions.

Vegetarians have lower rates of coronary artery disease, hypertension, non-insulin-dependent diabetes mellitus, some forms of cancer, and obesity than do nonvegetarians.[1] Vegetarians may also have fewer kidney stones and gallstones. Although lifestyle factors other than diet may have some bearing on health benefits, the vegetarian diet itself is likely a major factor. Plant-based diets are lower in total fat, saturated fat, and cholesterol than nonvegetarian diets, and they are higher in the protective substances found in plant matter, such as fiber and antioxidant nutrients. In fact, it is much easier to meet the dietary guidelines for Americans on a vegetarian diet than on a nonvegetarian diet.

Well-planned vegetarian diets easily meet nutritional requirements and dietary recommendations without providing the excess fat and cholesterol that characterize the traditional US nonvegetarian diet. Even so, many health professionals still have questions about some of the nutrients that we all learned to associate with animal sources. Most common among these are questions about protein, iron, calcium, vitamin B_{12}, vitamin D, and zinc.

Myths concerning protein needs and vegetarian diets prevail, although protein needs are the nutritional issue for which there is probably the least reason for concern. The fact is that all essential and nonessential amino acids can be supplied by plant sources alone, assuming that a

reasonable variety of foods is consumed and that calorie intake is adequate to meet energy needs. Assuming that these two criteria are met, it would actually be difficult to plan a protein-deficient diet. There is also no need for a conscious combining of foods within a given meal to form a "complete" protein, as the outmoded complementary protein theory suggested was necessary.

Concerns about iron nutriture center around the idea that animal (heme) sources of dietary iron are absorbed more easily than are plant (nonheme) sources of dietary iron. Some well-known inhibitors of dietary iron absorption are present in plant-based foods, such as phytates in grains or tannic acid in tea. (Dietary fiber does not bind with iron, as was once widely thought.)

Plant foods, however, also contain enhancers of dietary iron absorption, such as the ascorbic acid found in fruits and vegetables. Within the context of the total diet, these inhibitors and enhancers of iron absorption generally offset each other. In reality, vegetarians are no more prone to iron deficiency than are nonvegetarians.[1] An exception is some populations of vegetarians in developing countries who consume diets that are heavily grain-based with little access to vitamin C-rich produce and who, in some cases, drink copious amounts of tea. Western vegetarians, however, typically have good iron status.

Some substances found in plants also appear to inhibit the absorption of dietary calcium. Once again, however, within the context of the total diet this effect is apparently insignificant. Calcium deficiency in vegetarians is rare, and even when calcium intakes are below the recommended dietary allowance,[2] there does not appear to be an adverse health effect in vegetarians.

Vegetarians absorb and retain calcium better than do nonvegetarians. In fact, US calcium recommendations are considerably higher than those for populations that consume a more plant-based diet. The increased US calcium recommendations are designed to compensate for the calciuric effect of the high levels of animal protein intake that are customary in this country. Thus, while vegetarians generally consume adequate amounts of protein, they do tend to moderate their protein intake, resulting in more efficient calcium absorption.

Zinc is a trace mineral that is receiving more attention recently in the nutrition literature as its role in human growth and development is explored. Western vegetarians typically have satisfactory zinc status, however. Good plant sources of zinc include grains, nuts, and legumes.

Vitamin D is routinely added to the milk supply in the United States. Therefore, anyone who consumes dairy products is receiving a vitamin D supplement. Vitamin D is produced on the skin's exposure to sunlight and is stored by the body. Most people can get all of the vitamin D they need from regular exposure to sunlight. For those who consume no dairy products and who, for whatever reason, do not receive regular exposure to sunlight, an over-the-counter vitamin D supplement of no more than 100% of the recommended dietary allowance for vitamin D can be taken.

Granted, any dietary pattern—vegetarian or nonvegetarian—has the potential to be healthful or hazardous, depending on how much attention is paid to basic principles of nutrition. But reasonably planned vegetarian diets are appropriate for people of all ages and are associated with certain health advantages. Therefore, physicians and other health care providers should be educated about the health and nutritional aspects of vegetarian diets and be ready to support patients who express an interest in this dietary alternative. For this reason, the article by Randall White, MD, and Erica Frank, MD, MPH, elsewhere in this issue of the journal[3] is a valuable addition to the medical literature.

Planning vegetarian meals is simple. An excellent consumer education pamphlet, *Eating Well—The Vegetarian Way,* is available from the American Dietetic Association in bulk or in single copies. This 12-page brochure includes practical tips for planning vegetarian diets, an explanation of nutrition issues, a meal plan, and a sample menu. The meal plan starts with the vegan, or strictly vegetarian, diet as the "least common denominator" and can be adjusted to include some animal products as desired. Contact the American Dietetic Association at (312) 899-0040, or write to 216 West Jackson Blvd, Suite 800, Chicago, Illinois 60606-6995.

In summary, patients who initiate a discussion of vegetarian diets as a dietary alternative should be encouraged by their physicians and other health care providers to make this lifestyle change and supported by referrals to sources of good-quality reliable educational materials. Furthermore, physicians and other health care professionals should be aware of the potential health benefits of vegetarian diets and the relative lack of risk associated with appropriately planned vegetarian diets and offer this alternative as an option to their patients, particularly those who are at high risk for coronary artery disease.

Not everyone will be interested in making the switch to a vegetarian lifestyle. But everyone deserves to have the choice. If the choice is to adopt a more plant-based diet, then health care providers should encourage and support that decision.

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Meniscal Repair

To the Editor: The Epitomes, "Important Advances in Orthopedics," in the October 1993 issue, were exceptionally well done and balanced.[1] All the subjects were thoughtfully written with current information for both surgeons and nonsurgeons to better treat and counsel their patients. My congratulations to Dr McMaster, the advisory board, and all of the authors.

The subject of meniscal repair was particularly thought provoking.[2] Dr Colville's meniscal repair section was well organized and an excellent review of our current knowledge of the importance of preserving knee menisci. He reports 70% to 90% healing on second look after meniscal repair.

As a physician who has practiced from the "Total Meniscectomy Years" to the "Meniscal Repair Years," I am somewhat skeptical of dogma. Ciotta has reported on 40- to 60-year-old patients with anterior cruciate ligament injuries treated nonoperatively doing better than patients with reconstructed ligaments.[3] We reported a series of 48 recreational athletes with anterior cruciate ligament injuries treated without reconstruction.[4] With an average of five years' follow-up, only 15 (30%) required arthroscopic meniscectomy. One would expect a larger number of meniscus tears in these patients.[5]

Could some of these patients be healing their meniscal tears without surgical intervention? Do you think a delayed look at three to six months would reveal healing on these patients' meniscal tears?

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* * *

Dr Colville Responds

To the Editor: Peripheral tears within the vascular portion of the meniscus may heal without surgical intervention. Current common practice is not to repair peripheral meniscal tears that are stable and less than 1 cm in length. This practice is based on a consensus of opinion rather than scientific information. Larger meniscal tears and tears associated with anterior cruciate ligament injuries appear to be less likely to heal because of the increased stress at the site of injury. Older patients may have a lower incidence of late meniscectomy following anterior cruciate ligament injury. Whether this is due to healing of their meniscal tears or to decreased activity level in this group of older patients is unclear.

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Verapamil-Induced Hepatotoxicity

To the Editor: Verapamil hydrochloride, a calcium channel blocker, is widely used to treat hypertension, supraventricular tachycardia, and angina pectoris and is used for the prophylaxis of migraine and cluster headaches. Commonly reported adverse effects of verapamil use include constipation, dizziness, nausea, hypotension, headache, and edema. Verapamil-induced hepatic injury has been reported in six cases since 1981.[1-6] We report the case of another patient in whom symptoms of hepatitis developed with abnormal liver function while on verapamil therapy.

Report of a Case

The patient, a 50-year-old man with a history of chronic cluster headaches, was started on a regimen of verapamil sustained-release tablets, 240 mg a day. As his headaches did not abate after a month, the regimen was changed to immediate-release verapamil, 80 mg three times a day. Four weeks later, he had epigastric fullness and dark urine for one week. There was no change in appetite or stool color. He drank one or two beers every two to three weeks and had not had any for two weeks before his clinic visit. He had no history of hepatitis or injection-drug abuse and had no other risk factors for hepatitis. On examination, his liver was palpable 4 cm below the costal margin with a total span of 12 cm; it was moderately tender. There was questionable mild icterus. The results of the rest of the examination were unremarkable.

Liver function tests showed an alkaline phosphatase level of 533 U per liter (normal 34 to 110), aspartate aminotransferase 209 U per liter (normal 4 to 44), γ-glutamyltransferase 429 U per liter (normal 16 to 74), and total bilirubin 32 μmol per liter (1.9 mg per dl) (normal 5 to 26 μmol per liter). Abdominal ultrasonogram obtained the next day showed normal liver size and texture and biliary tract. Tests for hepatitis B surface antigen and core antibody, hepatitis A antibody, and hepatitis C antibody were negative.

The verapamil therapy was discontinued on the first visit, and a diagnosis of viral- or drug-induced hepatitis was considered before the liver test results were available. A week later, his symptoms were markedly improved, the liver was not palpable, and there was no epigastric or right upper quadrant tenderness. Liver function test results started to improve within a week, and by four weeks the

γ-glutamyltransferase level was 100 U per liter, total bilirubin 14 μmol per liter (0.8 mg per dl), alkaline phosphatase 129 U per liter, and aspartate aminotransferase 22 U per liter. We have not resumed verapamil therapy in this patient as we think that a mixed hepatocellular and cholestatic pattern of liver function abnormality was most probably due to the drug because all the symptoms resolved and abnormal liver function test results promptly returned to normal with its discontinuation.

Discussion

All other cases described in the literature had clinical features similar to those described in this patient: gastrointestinal discomfort, right upper quadrant tenderness, darkening of urine, and hepatomegaly. Abnormal values of liver function tests were mostly of mixed hepatocellular and cholestatic pattern. Two patients had liver biopsies that showed pronounced cholestasis in one[1] and mixed inflammatory cells with eosinophil-predominant infiltrates in portal tracts with moderate cholestasis in the other.[2] Patients' ages ranged from 47 to 61 years with equal sex distribution. Symptoms occurred from two to six weeks after verapamil therapy was started. Three patients were rechallenged (one accidentally), and liver function test results rapidly became abnormal, suggesting a hypersensitivity reaction to the drug.[1,3,4] Symptoms resolved quickly (within two weeks) with the discontinuation of verapamil in all patients. All authors and the manufacturer recommend periodic monitoring of liver function in patients for whom verapamil is prescribed. Whether this is being done in clinical practice and whether it is cost-effective for all patients receiving verapamil are still unanswered questions. Patients started on verapamil therapy should definitely be cautioned about symptoms of hepatitis, and they should be instructed to report these immediately to their primary care physician. Physicians need to be aware of this less-well-known adverse reaction to verapamil.

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Who Says Being a Doctor Is Still Fun?

To the Editor: "Is Being a Doctor Still Fun?" by Chuck and colleagues in the December 1993 issue[1] was interesting and provocative, especially during these times of uncertainty about the future of medicine—which translates to physicians' practice of medicine. The conclusion by the authors that it is still fun being a doctor seemed reasonable to me, until I looked at the response to one of their questions.

The answer to the statement, "I would encourage my child to pursue a career in medicine," produced a "yes" vote by only 44% of the respondents. If medicine is such a "fun" occupation, why are so few of us encouraging our kids to become physicians and partake of the fun? Is it because we do not want to share the fun with others? Perhaps we do not want the best for our own children. Is it possible that children of physicians are unsuited, either genetically or for some other reason, to practice medicine? There are also other possibilities to explain this type of response; the one that most concerns me, however, is that perhaps we physicians realize that our fates have been sealed and that we would rather have our children enter a nonmedical occupation that is truly more fun than the practice of medicine. If that is so, then this might cast some suspicion on the validity of this study, and the conclusion might be that it is not so much fun to practice medicine. A clarification by the authors could boost my morale, and I, too, could begin to have more fun.

Incidentally, I have teenaged children and would be thrilled to pieces if one of them found that the practice of medicine was in his or her future.

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To the Editor: The recent survey by Chuck and coworkers was interesting. Harold Osterud, MD, and I attempted a few years ago to pursue this question from a viewpoint that would reveal differences in two large groups of primary care practitioners—pediatricians and internists.[1] We attempted to measure job satisfaction by determining the attrition rate that might be the result of early retirement or career change in the two fields. Because there appeared to be so few pediatricians older than 60 years still practicing pediatrics, this perception seemed to warrant confirmation for physician supply studies and for counseling of medical students.

Our investigation yielded a response rate of 82% in a study group of 181 physicians. The study group was limited to physicians born before 1926. Job satisfaction findings were similar to the figures offered by Chuck and colleagues. More than 70% of pediatricians and internists would encourage a qualified student to pursue the study

of medicine. Of the internists, however, 76% indicated that they would once again select internal medicine, but only 44% of the pediatricians would make the same choice. An additional fact emerged, confirming our initial perception. In the age group 60 to 65 years, 83% of the nonretired internists were still practicing primary care internal medicine, but only 11.5% of the nonretired pediatricians were involved in the practice of primary care pediatrics. Our figures were derived only from physicians in Oregon, but the implications for physician supply are obvious. We attempted to unravel the questions and answers to explain our findings, but would like to learn of larger studies being designed.

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* * *

To the Editor: I found the article by Chuck and associates thought-provoking, but I think these authors present an unduly optimistic portrayal of American physicians' viewpoints: They see the glass as half full, and I find it half empty.

In the introduction, the authors cite other polls[1] that found that only 60% of physicians interviewed would definitely or probably enter medical school again. The authors' 67% positive response to an equivalent question is a result that they feature but that seems similar to me. Their results are derived from responses in the three positive categories of a 7-point scale (including responses that were only mildly positive).

I find it most distressing that even with the best possible interpretation of the data, only 63% of respondents believed that their job was "fun"—a statistic they define as "a solid majority." Conversely, 37% of the physicians questioned do not find their job fun, 37% do not find their job prestigious, and 33% would not choose to enter medicine again.

The authors report that 40% were not satisfied with their amount of night and weekend duty, 53% to 55% believed they had no control over their work environment or the hours they worked, and 55% were concerned about contracting a serious infection such as the acquired immunodeficiency syndrome at work. Even more depressing was their finding—not commented on by them—that 56% would not encourage their children to pursue a career in medicine.

The authors believe the severity and effect of "the recent demoralization of the medical profession . . . have been overstated." Their data could be interpreted to show exactly the opposite—that many physicians have considerable problems with their profession, that they wish they were in another profession, and that they hope their children will not follow in their footsteps.

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* * *

Drs Chuck and Nesbitt respond

To the Editor: Any study of job and career satisfaction needs to be interpreted in both absolute and relative terms. For example, our data showed that 67% of respondent physicians would choose their careers again. Viewed in absolute terms, this seems like a respectable figure. Viewed in relative terms, it seems even more notable considering that only 44% of respondents in a random survey of working adults would choose their line of work again (Gallup Poll for Accountants on Call, May 1988). Expecting 100% of physicians to say that they would choose their careers again would be analogous to expecting a major league batting champion to hit 1.000—nice, but unrealistic.

The fact that only 44% of physicians would encourage their children to pursue a career in medicine is interesting because one might expect this figure to more closely approximate the 67% of physicians who would choose medical careers again for themselves. This could be attributed partly to physicians believing that "our fates have been sealed" or are, at best, unclear at this time. It may also be a result of a generation of parents who have been admonished not to pressure their children into anything, be it ballet lessons, a particular college, or a career. We suspect that the 44% figure would have been higher if we had clarified the question to read: "If your child expressed an interest in a medical career, would you encourage him or her to pursue this interest?" Of note, when a similar question was posed to attorneys by *California Lawyer* magazine in 1992, only 27% of respondents said they would advise their children to become lawyers ("It's Becoming a Miserable Profession"—Monthly Facts Poll, *California Lawyer*, March 1992, p 96).

Being in primary care ourselves, we are sensitive to Dr Schunk's concerns about physician satisfaction and attrition rates in the primary care fields. He may be encouraged that when we looked at Permanente Medical Group pediatricians, 64% said they would choose their specialty again. In addition, our primary care respondents showed equal overall job satisfaction when compared with their specialty colleagues. Still, we do recognize that there are many entrenched inequities within the medical profession, especially as related to education in medical schools and compensation, that have made the fields of pediatrics, internal medicine, and family practice less desirable to medical students and less remunerative for practicing physicians. For this reason, we strongly believe that current health care reform efforts that emphasize an expanding role for primary care physicians also need to address and correct these inequities. Only then can we expect to recruit and retain some of the best and brightest to the front lines of medicine.

With regard to our analysis of the data as seeing "the glass half full" as opposed to half empty, we plead guilty;

however, we do not think that seeing the glass half full equates with presenting "an unduly optimistic portrayal of American physicians' viewpoints." In fact, we would argue that up until this time, physicians and the media have painted an unduly pessimistic picture of what it is like to be a physician today. As a colleague recently wrote to us, "We tend to be louder wailing than laughing." The truth is that for most of us, the benefits of helping patients and having meaningful relationships with them continue to outweigh the hassles posed by challenges to our autonomy and professional satisfaction. We would rather savor the half glass of milk that remains than lament over the half glass that is missing.

It is encouraging that despite negative publicity about our profession, applications to medical schools continue to rise. Talented young persons, presented with a wide menu of fascinating and challenging careers, are opting for medicine in record numbers. Preliminary data from a survey of premedical students suggest that these applicants have realistic expectations of what a medical career would be like (J. Chuck, MD, P. Van Houten, PhD, Office of Career and Graduate School Services, University of California, Berkeley, unpublished data, 1993). In addition, a large number of established professionals continue to leave their jobs to become physicians. In interviewing this type of applicant to our medical school, we often hear comments like, "I want to help people on a one-on-one basis and to see the results of my efforts." We challenge practicing physicians to critically compare and contrast their current profession with others that they might have pursued or would consider pursuing in the future. We think most will conclude that, all things considered, the grass is greenest on our side of the fence where every patient interaction gives us the opportunity to help our fellow humans in an important and meaningful way.

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Are Performers Special Patients?

To the Editor: We wish to comment on the review, "Performing Arts Medicine," by Ostwald and colleagues in the January 1994 issue.[1] As primary care physicians, we appreciate this information because understanding the special problems of performers will enhance the accuracy of our diagnoses and increase the likelihood of rapid, appropriate therapy for our patients.

Unfortunately, the implication in the authors' discussion of upper respiratory tract illnesses and allergies among singers cannot go unchallenged. They discourage a wait-and-see approach and advocate quick intervention because of the level of anxiety that artists experience and because of the possibility of a canceled performance. We cannot agree that artists are entitled to more rapid or—allegedly—superior health care than our other patients who also face time off work or other equally good reasons to avoid the inconvenience of self-limited illness. All our patients deserve the best we have to offer each time we see them, independent of their livelihood.

We are disturbed by the authors' suggestion that we should use powerful broad-spectrum antibiotics to manage ailments that are almost entirely viral or allergic in origin. Is there evidence that performers respond better than other people when given a broad-spectrum antibiotic for a cold?

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* * *

Drs Ostwald, Baron, Byl, and Wilson Respond

To the Editor: We were happy to read the appreciative response to our recent article on performing arts medicine; however, Drs Kennedy and Shearn appear to have misinterpreted our comments regarding the care of vocal performers. Efficient and rapid treatment of a singer or actor does not imply that performing artists deserve superior health care. The approach is patient-specific, as it always should be with good medicine. We point out that singers and actors are in fact affected very differently by sinusitis or acute laryngitis than patients with another livelihood. Such conditions may not mean time off work for the latter, nor do throat problems necessarily imperil the career of a nonsinger.

Regarding comments about antibiotics, we mention in a general sense that amoxicillin clavulanate or cephalosporins are appropriate for some illnesses such as sinusitis and laryngopharyngitis, which are often bacterial. We did not intend to suggest that these medicines be used to treat a cold.

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Recurrent Nonsuppressible Secondary Hyperparathyroidism Following Subtotal Parathyroidectomy

To the Editor: We report a case of severe, recurrent, secondary hyperparathyroidism. Although subtotal parathyroidectomy is typically advocated for patients with uremia,[1] close postoperative surveillance is crucial: nonsuppressible secondary hyperparathyroidism is a potentially life-threatening condition in these patients.

Report of a Case

The patient, a 28-year-old woman, was transferred to

our hemodialysis center with refractory anemia, hypertension, and general aching. She began hemodialysis in 1980 for end-stage medullary sponge kidney disease. Over the next 13 years, the patient rejected three renal allografts and was treated with hemodialysis with fair metabolic control.

A subtotal (3½ gland) parathyroidectomy was done in 1987. Both native kidneys and all allografts were removed because of hypertension and complications of rejection.

Our evaluation confirmed the presence of hypertension resistant to the concurrent administration of hemodiafiltration, metoprolol tartrate, clonidine, nifedipine, and enalapril maleate. The hematocrit was 0.23 (23%), and transferrin saturation was 0.25 (25%). Despite a regimen of erythropoietin, 5,000 units intravenously three times a week, the patient remained anemic. The calcium-phosphorus product (milligrams per deciliter of calcium times milligrams per deciliter of phosphorus) was 50, but the serum alkaline phosphatase level was 762 U per liter (normal < 117), suggesting recurrent hyperparathyroidism. The serum intact-parathyroid hormone level was 5,576 pg per ml (1,360 pmol per liter; upper limits of normal, 54 pg per ml). Despite the intravenous administration of calcitriol, 2 μg per treatment, phosphate binding, phosphate restriction, and dialytic therapy for three months, the hyperparathyroidism was not suppressed.

Neck re-exploration revealed a 3.5-cm solitary parathyroid mass, which was resected. Histopathologic examination revealed parathyroid adenoma. Massive calcium supplementation was required—more than 250 grams cumulative dose of calcium gluconate and calcium carbonate—over the next several weeks to maintain normocalcemia. The patient required intensive care monitoring for severe neuromuscular, cardiovascular, and electrocardiographic complications of hypocalcemia.

The patient ultimately became stable on a regimen of calcitriol, 0.5 μg; calcium acetate, 1,300 mg; and calcium carbonate, 1,500 mg per day.

By four weeks after the operation, the patient's general aching abated, her blood pressure was 150/90 mm of mercury with low-dose nifedipine therapy plus hemodiafiltration, and her hematocrit value improved, implying a recovery of erythropoietin sensitivity. At three months and nine months after the operation, intact parathyroid hormone levels were less than 5 pg per ml, suggesting adequate removal of residual parathyroid tissue.

Comment

Severe, nonsuppressible secondary hyperparathyroidism recurred in this patient despite standard therapy. The remnant half of the original native parathyroid gland enlarged to a massive adenoma. A typical "hungry bone" syndrome[2(p1441)] occurred postoperatively, reflecting the severe preoperative hyperparathyroidism.

The patient's preoperative condition suggested erythropoietin resistance[3] associated with the osteosclerosis of secondary hyperparathyroidism. Refractory hypertension may have reflected vascular smooth muscle intracellular calcium overload.[4] This is likely, rather than erythropoietin-induced hypertension, because of easier blood pressure control after the parathyroidectomy.

Some remaining parathyroid hormone activity may help prevent osteomalacia in uremic patients,[5] so subtotal parathyroidectomy may be a first-line treatment. The central importance of anemia as a predictor of mortality, however,[6] and the potential of parathyroid hormone to cause erythropoietin resistance demand early surgical intervention with remnant parathyroidectomy when parathyroid disease recurs.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

The Final Question

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When we search for a lost object, we often find it in the last place we look. So it is that in talking with patients, often the most important answer comes only in response to the final question asked.

Tanya was a 12-year-old—unmarried, pregnant, a dropout. She lived and worked on the streets. Apart from cocaine use and secondary syphilis infection, her prenatal course was uncomplicated. Her labor and delivery went well, although her 32-year-old boyfriend was not there for support. When I discharged her from the hospital on the third postpartum day, I was concerned about her ability to cope with and care for her newborn son. I asked her to come to the office in a week, earlier than usual because I was worried about this high-risk mom and her higher-risk baby.

One week later she returned with her happy, healthy, well-dressed, and, to all appearances, well-cared-for baby. My concern continued despite the reassuring appearances. As always, I asked, "Any questions or problems?" "No," she assured me. I asked several more times during the well-baby examination, "Any concerns?—Any worries?—Anything you'd like to ask me?" She repeatedly assured me that she had no questions at all about caring for her new baby. I was still worried. Perhaps she did not know enough or was too embarrassed to ask any questions. How could this young woman—this girl, really—feel so confident and comfortable with the challenge of her first baby? How, indeed, when mothers with so much more education, prenatal preparation, family support, and resources had so many questions and so much insecurity?

I asked her a few questions to explore the limits of her knowledge. "What are you doing to take care of the baby's cord? How do you know when he has had enough to eat? What works best when your baby cries?" She had all the answers, it seemed.

My lingering doubts prompted me to confront her with one last question: "How come you know so much about babies?"

"Are you kidding?" she replied. "I have six older sisters. Every one of them has kids. Who do you suppose took care of all those little babies? My mother and me, that's who."

I realized that this 12-year-old, despite all of her social and medical risk factors, did, indeed, have more experience caring for babies than did any of my patients with prenatal classes, professional careers, and PhDs. In assessing her risk factors, I had not realized that some strengths came from surviving the difficult life she had led so far.

* * *

Physicians know how easy it is to underestimate how much a patient drinks. I was alert to this pitfall when interviewing Patrick, an engaging Irishman with a wee bit of high blood pressure, obesity, liver enzyme test abnormalities, and a motor-vehicle accident or two. He was a professional musician, which seemed like a definite risk factor to me, so I pursued this line of inquiry.

"How much do you drink?" I asked, as always.

"Not very much," he answered, as always.

"How much is that?" I asked, hoping for an honest answer to my question.

"Not nearly as much as I used to drink." It became clear that I would have to earn progress in small increments.

"What do you drink?"

"Oh, only beer. That hard stuff isn't good for you," he assured me.

"How often do you drink beer?" I continued.

"Only when I play music with the band."

We were now developing a rhythm of give and take. We were beginning to get somewhere. His answers so far, however, convinced me that I was not wasting my time with this repartee.

"How often do you play music?" seemed like the next logical step.

"Six nights every week," he replied enthusiastically.

Now I zeroed in on my goal: "How much beer do you drink on a typical night playing with the band?"

"Oh, I drink about six. But that's down from what I used to put away. I used to drink eight or nine on most nights. But that's not an awful lot; all the guys in the band drink beer like that. I don't have any problem; I drink less than most of them."

"That's a lot of beer," I responded, with more interest than alarm. "How do you get much music played? You guys must be going to the bathroom all the time."

"That's why Irish dance tunes are only three minutes long," he admitted.

For my last question I turned to the restatement stratagem. "Let me see if I've got this right. You drink six beers a night, six nights a week," I summarized, feeling that I had at last gotten a measure of this man and his problems.

(Phillips WR: The final question. West J Med 1994; 160:490-491)

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"No," he blurted. "Quarts."

He was almost as surprised as I was. Now we were talking "big time" beer consumption and, at last, we began to make progress on his related medical problems.

* * *

Sometimes patients play the game of cat and mouse for some reason of their own. While working temporarily in an outpatient clinic, I encountered such a young woman. She had come in with abdominal pain, which led me to take a gynecologic history. All went smoothly until I asked my routine question.

"What do you do for contraception?" I asked.

"Nothing."

"Are you sexually active now?"

"Yes."

"Do you want to get pregnant?"

"No."

Now I thought I had come upon a new problem: a patient at risk for unplanned pregnancy. As a family physician, I turned off the avenue of abdominal pain and onto the family planning path.

"Are you concerned about the possibility of getting pregnant?"

"No," she answered. Something told me that something was being left unsaid. Now was the time to step back a bit and try the open-ended question.

"How is that?"

"I know I won't get pregnant," she asserted boldly.

I have heard the same self-assured statement often enough before to think that I was helping by pursuing the matter even further.

"How do you know you will not get pregnant?" I asked with genuine interest. I would have dropped the matter if she had simply said that she was not concerned about contraception and that we should get on with the saga of her undiagnosed abdominal pain. I was on track, however, and she seemed to want to drag the bait ahead of me a little further. So I followed.

"Do you think you are infertile?" I inquired.

"No," she answered, and then waited for my next question.

What was she trying to tell me with these answers? No doubt I had not asked the right question to understand this woman's message. Now we were both waiting for the denouement.

Again I turned to restatement, almost as if thinking aloud. "Let me see. You are having sex regularly. You believe you are fertile. You use no contraceptive method at all. And you feel comfortable that you have no risk of getting pregnant. Am I right so far?" I asked her.

"Yes," she said, breaking a bit of a smile that finally displayed her enjoyment of this game.

The final question then came to me: "Are your sexual partners male?"

"No," she said simply.

"I understand," was my reply. She had set out to teach a lesson to a stranger. In the resulting give-and-take, we developed a patient-physician relationship. Together we eventually diagnosed and cured her abdominal pain.

* * *

The artful medical history can become a helping interview. Sometimes it can help both physicians and patients better understand each other and themselves.

Lessons From the Practice

To Err Is Human

MICHAEL J. McCLURE, MD, PhD, *Salt Lake City, Utah*

I well recall the first day of my general surgery rotation as a third-year medical student. I was assigned to the local Veterans Affairs hospital. All of the medical students working at that particular hospital met at the main nurses' station at 7:30 in the morning. The interns and residents were all too busy to show us our respective duties, so we just stood around, nervously wondering what we were supposed to be doing.

While we were waiting, one of the junior residents walked up.

"Anybody know how to remove staples?" he asked the group at large.

After a moment's hesitation, I responded that I had removed staples before.

"Good. Get a staple remover from one of the nurses and remove Mr Jones's staples in Room 406."

I felt relieved to be productively occupied. The waiting was becoming nerve-wracking. I had only removed staples a few times before, but it had not seemed to be a big deal. I found the necessary tool and some gloves and went to Room 406 to do as I had been told.

"Mr Jones?" I asked as I entered the semiprivate room. The middle-aged man looked up at me and said, "Yes."

I told him I had been sent to remove his staples. I proceeded to do so and then covered the wound with sterile adhesive tape and a light dressing. On leaving the room, I ran into the junior resident who had given me this assignment.

"Have you removed Mr Jones's staples?" he inquired.

"Yes," I responded. "I just finished."

"No, you haven't," he said. "Mr Jones is standing over there. You removed staples from Mr Smith, his roommate. Mr Smith is in his first day postop from an appendectomy."

Words cannot describe the feeling of horror that I had at that moment. Mr Smith's staples should not have been removed for several more days. I had visions of him coughing and his bowels popping out through the wound. Furthermore, I had only been on the service for about 30 minutes, and I had already done a major screwup!

It turned out that Mr Smith was hard of hearing, but refused to wear his hearing aid. No matter what was said to him, he would answer "Yes."

Fortunately, the junior resident was an exceedingly kind person. We assured ourselves that the Steri-Strips that I had put on the wound were done well and then closely observed the situation over the next several days. Mr Smith recuperated without complications and was discharged several days later.

I have thought about this mistake many times. I well recall the feelings of unworthiness and the resultant fear of making even more serious mistakes. Being just a little bit wiser now, I recognize that this is an aspect of the human condition. We all know that we make mistakes, and it is unreasonable to delude ourselves otherwise. And yet, as physicians, we do not have the luxury of making errors.

Physicians are therefore faced with a dichotomy. To err is human. Physicians may not err. Therefore, physicians may not be human. Is this faulty reasoning the basis of why so many physicians consider themselves to be deities? Is it also the basis for our litigious society demanding compensation when we do not live up to their expectations of perfection?

I have learned to accept my own imperfection. It helps to keep me humble. It also serves to reinforce my desire to learn more about the art and science of medicine so that potential mistakes can be avoided. Rather than wanting to cover up or deny this mistake, I treasure it. This was one of the most educational experiences I have ever had.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(McClure MJ: To err is human. West J Med 1994; 160:492)

From the University of Utah School of Medicine, Salt Lake City. Dr McClure is now with the Department of Psychiatry and Neurology, Eisenhower Army Medical Center, Fort Gordon, Georgia.

Reprint requests to Michael J. McClure, MD, PhD, 548 Brandermill Rd, Evans, GA 30809.

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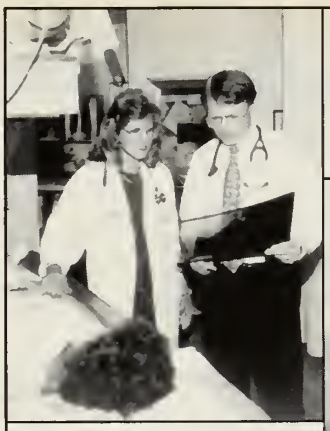

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(Continued from Page 497)

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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-7, 1995, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 7-11, 1994, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 7-9, 1994, Ritz-Carlton Maunalani, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 28-30, 1994, Sun Valley.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1994, Holiday Inn, Great Falls.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1995, date and location to be announced.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1995, date and location to be announced.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-24, 1994, University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 22-24, 1994, Wenatchee.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 9-11, 1994, Jackson Lake Lodge, Moran.

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For Efficacy As Maintenance Therapy In Healed Duodenal Ulcer Disease

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets hs

Please see references and brief summary of Prescribing Information below.

The safety profile of ZANTAC is confirmed in over 13 years of use and over 190 million patient treatments worldwide.* Low incidence of side effects. Headache, sometimes severe, was most frequently reported in controlled clinical trials, with an incidence rate not significantly different from placebo.[3]

*Estimate, Glaxo Inc.

References: 1. Silvis SE, Griffin J, Hardin R, et al. Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer. *J Clin Gastroenterol.* December 1985;7:482-487. **2.** Gough KR, Korman MG, Bardhan KD, et al. Ranitidine and cimetidine in prevention of duodenal ulcer relapse: a double-blind, randomised, multicentre, comparative trial. *Lancet.* September 22, 1984;2:659-662. **3.** Data on file, Glaxo Inc.

Zantac® 150 Tablets **BRIEF SUMMARY**
(ranitidine hydrochloride)
Zantac® 300 Tablets
(ranitidine hydrochloride)
Zantac® Syrup
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of active duodenal ulcer.
2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of active, benign gastric ulcer.
5. Treatment of gastroesophageal reflux disease (GERD).
6. Treatment of endoscopically diagnosed erosive esophagitis.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug or any of the ingredients.

PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.
3. Rare reports suggest that Zantac may precipitate acute porphyric attacks in patients with acute porphyria. Zantac should therefore be avoided in patients with a history of acute porphyria.
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.
Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.
Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks.
Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.
Pediatric Use: Safety and effectiveness in children have not been established.
Use in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.
Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.
Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.
Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.
Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.
Musculoskeletal: Rare reports of arthralgias and myalgias.
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.
Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported.

When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

Studies in dogs receiving dosages of Zantac® in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)
Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.
Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.
Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.
GERD: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.
Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) four times a day.
Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

June 1993
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Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.

Zantac® 150 Tablets/Zantac® 300 Tablets:
Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
Zantac® Syrup:
Manufactured for Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
by Roxane Laboratories, Inc., Columbus, OH 43216

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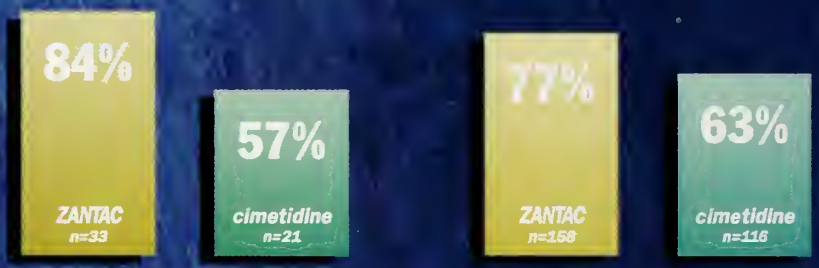
For Efficacy As Maintenance Therapy In Healed Duodenal Ulcer Disease

PROVEN SUPERIORITY

ZANTAC 150 mg h.s. superior to cimetidine 400 mg h.s. for maintenance therapy of healed duodenal ulcer disease at 1 year.[1,2]



P=0.01. Adapted from Silvis et al.[1*†]

P=0.004. Adapted from Gough et al.[2*]

*These trials used the currently recommended dosing regimens of ZANTAC (150 mg h.s.) and cimetidine (400 mg h.s.). A comparison of other dosing regimens has not been studied. The studied dosing regimens are not equivalent with respect to the degree and duration of acid suppression or suppression of nocturnal acid. The superiority of ZANTAC over cimetidine in these trials indicates that the dosing regimen currently recommended for cimetidine is less likely to be as successful in maintenance therapy.

†Percent estimates are determined by life-table estimates. If crude-rate estimates were used, percentage of patients ulcer free after 1 year would be 88% for ZANTAC and 71% for cimetidine. All patients were permitted p.r.n. antacids for relief of pain.

The safety profile of ZANTAC is confirmed in over 13 years of use and over 190 million patient treatments worldwide.† Low incidence of side effects. Headache, sometimes severe, was most frequently reported in controlled clinical trials, with an incidence rate not significantly different from placebo.[3]

†Estimate, Glaxo Inc.

In DU Maintenance Therapy

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets hs

Please see references and brief summary of Prescribing Information on adjacent page.

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Glaxo/Roche Research Triangle Park, NC 27709

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Discover The Elegance Of A Hybrid

At first glance, it's the beauty of the hybrid Lily that catches the eye. The vibrant color. The delicately shaped petals. But study it more closely, and its *elegance* becomes apparent–a gentle blend of softness and strength.

At first glance, it's the enhanced performance of Vaseretic® that catches the eye. But study Vaseretic® more closely, and its *elegance* becomes apparent. The way its one-tablet, once-a-day dosage minimizes multiple medications. Minimizes the number of insurance copayments. And minimizes potassium supplementation.

A hybrid blending of tolerability and power that's available for the right patient. Vaseretic® is indicated for the treatment of hypertension in patients for whom combination therapy is appropriate.

And an elegant discovery for your practice.

VASERETIC® 10-25 *Next*

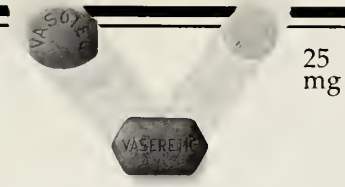
Enalapril Maleate-Hydrochlorothiazide

Vaseretic® is contraindicated in patients who are hypersensitive to any component of this product or to other sulfonamide-derived drugs and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Dosage must be individualized; the fixed combination is not for initial therapy.
Evaluation of the hypertensive patient should always include assessment of renal function.
For a Brief Summary of Prescribing Information, see adjacent pages.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*

TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*



10 mg

25 mg

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General; Enalapril Maleate; Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions,* and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide).*

Pregnancy; Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality,* below.)

Enalapril Maleate; Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats, and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide; Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General; Enalapril Maleate; Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions.)*

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium).*

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather, appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium, this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients; Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions; Enalapril Maleate; Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide; When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution

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assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse bone marrow assay.
Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.
Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.
There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.
Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.
Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.
Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.
Pregnancy; Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*
Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.
The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).
Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.
Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)
Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)
Cough: See PRECAUTIONS, *Cough.*
Clinical Laboratory Test Findings; Serum Electrolytes: See PRECAUTIONS.
Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)
Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.
Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.
Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.
Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.
Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established. *Nervous System/Psychatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.
Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.
Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*
Hydrochlorothiazide—Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg

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i-'pit-ə-mē\ *n* [L, fr. Gk *epitomē*, fr. *epitemnein* to cut short, fr. *epi-* + *temnein* to cut — more at TOME] (1520) **1 a :** a summary of a written work **b :** a brief presentation or statement of something **2 :** a typical or ideal example: EMBODIMENT (the British monarchy itself is the ~ of tradition —Richard Joseph) **3 :** Plural — *Epit-o-mes* — A regular FEATURE of *The Western Journal of Medicine*, now available in a single, bound volume.

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Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

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Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

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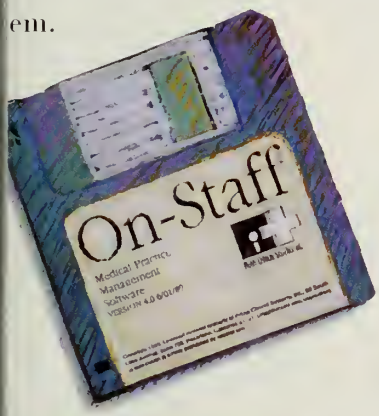

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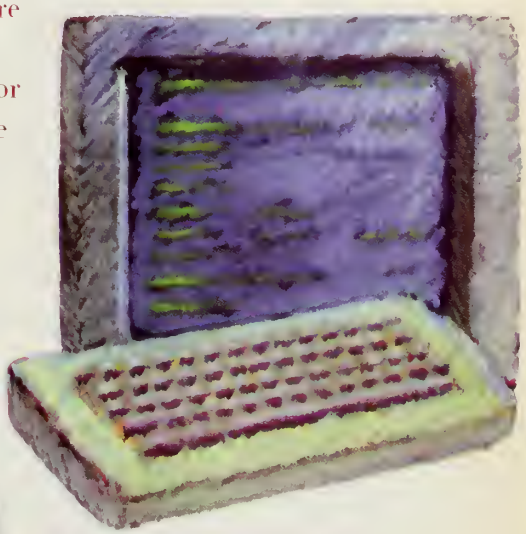

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REFERENCES:

1. Britton JW, Fajardo JE, Krafte-Jacobs B. Clinical and laboratory observations: Comparison of mupirocin and erythromycin in the treatment of impetigo. *J Pediatr.* 1990,117 B27-B29
2. *Bactroban* prescribing information.
3. McLinn S. A bacteriologically controlled, randomized study comparing the efficacy of 2% mupirocin ointment (Bactroban) with oral erythromycin in the treatment of patients with impetigo. *J Am Acad Dermatol.* 1990;22 883-885.
4. Rice TD, Duggan AK, DeAngelis C. Cost-effectiveness of erythromycin versus mupirocin for the treatment of impetigo in children. *Pediatrics.* 1992;89:210-214

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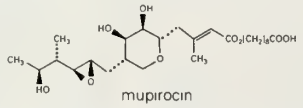
DESCRIPTION

Each gram of *Bactroban* Ointment 2% contains 20 mg mupirocin in a bland water miscible ointment base (polyethylene glycol ointment, N.F.) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The chemical name is (*E*)-(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid. The chemical structure is:



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CLINICAL PHARMACOLOGY

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Application of ^{14}C-labeled mupirocin ointment to the lower arm of normal male subjects followed by occlusion for 24 hours showed no measurable systemic absorption (<1.1 nanogram mupirocin per milliliter of whole blood). Measurable radioactivity was present in the stratum corneum of these subjects 72 hours after application.

Microbiology: The following bacteria are susceptible to the action of mupirocin *in vitro*: the aerobic isolates of *Staphylococcus aureus* (including methicillin-resistant and β-lactamase producing strains), *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, and *Streptococcus pyogenes*.

Only the organisms listed in the INDICATIONS AND USAGE section have been shown to be clinically susceptible to mupirocin.

INDICATIONS AND USAGE

Bactroban (mupirocin) Ointment is indicated for the topical treatment of impetigo due to: *Staphylococcus aureus*, beta-hemolytic *Streptococcus**, and *Streptococcus pyogenes*.

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components.

WARNINGS

Bactroban Ointment is not for ophthalmic use.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with the use of *Bactroban* Ointment, treatment should be discontinued and appropriate alternative therapy for the infection instituted.

As with other antibacterial products prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

Bactroban is not formulated for use on mucosal surfaces. Intranasal use has been associated with isolated reports of stinging and drying.

Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol-based ointments, *Bactroban* should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at systemic doses, i.e., orally, subcutaneously, and intramuscularly, up to 100 times the human topical dose and have revealed no evidence of impaired fertility or harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether *Bactroban* is present in breast milk. Nursing should be temporarily discontinued while using *Bactroban*.

ADVERSE REACTIONS

The following local adverse reactions have been reported in connection with the use of *Bactroban* Ointment: burning, stinging, or pain in 1.5% of patients; itching in 1% of patients; rash, nausea, erythema, dry skin, tenderness, swelling, contact dermatitis, and increased exudate in less than 1% of patients.

DOSAGE AND ADMINISTRATION

A small amount of *Bactroban* Ointment should be applied to the affected area three times daily. The area treated may be covered with a gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

HOW SUPPLIED

Bactroban (mupirocin) Ointment 2% is supplied in 1 gram Single Unit Packages of 50 and in 15 gram and 30 gram tubes.

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NDC 0029-1525-22 (15 gram tube)
NDC 0029-1525-25 (30 gram tube)

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In Memoriam

California Medical Association

ABRAMS, ALAN LOUIS, San Francisco. Died Jan 6, 1994, aged 77. Graduate of Stanford University School of Medicine, Stanford, California, 1941. Licensed in California in 1941. Dr Abrams was a member of the San Francisco Medical Society.

❧

ADAMS, GLENN D., Redlands. Died Feb 18, 1994, aged 62. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1957. Licensed in California in 1962. Dr Adams was a member of the San Bernardino County Medical Society.

❧

BAERNSTEIN, HARRY D., Jr, Upland. Died Mar 15, 1994, aged 66. Graduate of University of Wisconsin Medical School, Madison, 1949. Licensed in California in 1961. Dr Baernstein was a member of the San Bernardino Medical Society.

❧

BLANKENSHIP, JOHN R. S., La Jolla. Died Mar 1994, aged 67. Graduate of University of California, Los Angeles, School of Medicine, 1958. Licensed in California in 1959. Dr Blankenship was a member of the San Diego County Medical Society.

❧

CONLEY, JOHN W., Orange. Died Mar 7, 1994, aged 71. Graduate of Loyola University, Stritch School of Medicine, Maywood, Illinois, 1947. Licensed in California in 1948. Dr Conley was a member of the Orange County Medical Association.

❧

CORRY, MELVIN J., Paradise. Died Feb 4, 1994, aged 70. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1956. Licensed in California in 1964. Dr Corry was a member of the Butte-Glenn Medical Society.

❧

DANFORTH, MICHAEL A., Fullerton. Died Feb 4, 1994, aged 53. Graduate of University of Osteopathic Medicine and Health Sciences, Des Moines, Iowa, 1973. Dr Danforth was a member of the Orange County Medical Association.

❧

DE GENARO, FRANK, La Jolla. Died Jan 18, 1994, aged 52. Graduate of College of Medicine and Dentistry of New Jersey, Newark, 1967. Licensed in California in 1969. Dr De Genaro was a member of the San Diego County Medical Society.

❧

DOANE, CLARMONT P., Fresno. Died Apr 7, 1994, aged 89. Graduate of Washington University School of Medicine, St Louis, Missouri, 1933. Licensed in California in 1934. Dr Doane was a member of the Fresno-Madera Medical Society.

ELDEN, HAROLD, San Diego. Died Feb 3, 1994, aged 84. Graduate of Northwestern University Medical School, Chicago, Illinois, 1936. Licensed in California in 1945. Dr Elden was a member of the San Diego County Medical Society.

❧

FARRER, JOHN F., Newport Beach. Died Feb 20, 1994, aged 67. Graduate of Boston University School of Medicine, Boston, Massachusetts, 1953. Licensed in California in 1956. Dr Farrer was a member of the Orange County Medical Association.

❧

HORN, BERNARD, Vallejo. Died Mar 14, 1994, aged 71. Graduate of University of California, San Francisco, School of Medicine, 1953. Licensed in California in 1954. Dr Horn was a member of the Solano County Medical Society.

❧

JAMES, HAROLD E., Deer Park. Died Mar 17, 1994, aged 88. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1952. Dr James was a member of the Napa County Medical Society.

❧

LAVOIE, PAUL E., San Francisco. Died Jan 23, 1994, aged 61. Graduate of Hannemann Medical College of Philadelphia, Pennsylvania, 1969. Licensed in California in 1987. Dr Lavoie was a member of the San Francisco Medical Society.

❧

MCCASLINE, RAYMOND E., Pauma Valley. Died Jan 16, 1994, aged 89. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr McCasline was a member of the Orange County Medical Association.

❧

MILLS, RICHARD G., San Diego. Died Apr 1994, aged 64. Graduate of University of Michigan Medical School, Ann Arbor, 1955. Licensed in California in 1958. Dr Mills was a member of the San Diego County Medical Society.

❧

MOLITOR, JOHN J., Orange. Died Feb 27, 1994, aged 67. Graduate of Loyola University, Stritch School of Medicine, Maywood, Illinois, 1952. Licensed in California in 1953. Dr Molitor was a member of the Orange County Medical Association.

❧

PALMERTON, CALSON D., Escondido. Died Jan 19, 1994, aged 68. Graduate of McGill University Faculty of Medicine, Montreal, 1962. Licensed in California in 1964. Dr Palmerton was a member of the San Diego County Medical Society.

POMEROY, IRA L., Garden Grove. Died Jan 31, 1994, aged 70. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Pomeroy was a member of the Orange County Medical Association.

❧

POORE, THOMAS, Redwood City. Died Mar 14, 1994, aged 76. Graduate of University of Minnesota Medical School, Minneapolis, 1943. Licensed in California in 1948. Dr Poore was a member of the San Mateo County Medical Association.

❧

REEVES, JAMES E., San Diego. Died Feb 2, 1994, aged 86. Graduate of Emory University School of Medicine, Atlanta, Georgia, 1930. Licensed in California in 1936. Dr Reeves was a member of the San Diego County Medical Society.

❧

SCOTT, MERRILL B., Fresno. Died Mar 31, 1994, aged 67. Graduate of University of Illinois College of Medicine, Chicago, 1958. Licensed in California in 1959. Dr Scott was a member of the Fresno-Madera Medical Society.

❧

VARGAS, CARLOS A., San Francisco. Died Jan 16, 1994, aged 65. Graduate of U/Nat'l Autonoma Nicaragua, Leon, 1959. Licensed in California in 1964. Dr Vargas was a member of the San Francisco Medical Society.

❧

WEISS, HARRY A., Vista. Died Mar 3, 1994, aged 81. Graduate of Loyola University, Stritch School of Medicine, Maywood, Illinois, 1942. Licensed in California in 1947. Dr Weiss was a member of the San Diego County Medical Society.

Denver Medical Society

WESTERLUND, MARGARET E. Died Feb 15, 1994, aged 70. Graduate of University of Colorado School of Medicine, Denver, 1952. Licensed in Colorado in 1953.

New Mexico Medical Society

BARTON, AMY S., Carizozo. Died Mar 27, 1994, aged 82. Graduate of University of Michigan Medical School, Ann Arbor, 1937. Licensed in New Mexico in 1972. Dr Barton was a member of the Lincoln County Medical Society.

❧

GORDON, GREGORY A., Santa Fe. Died Oct 28, 1993, aged 47. Graduate of University of California, Los Angeles, School of Medicine, 1966. Licensed in New Mexico in 1982. Dr Gordon was a member of the Santa Fe County Medical Society.

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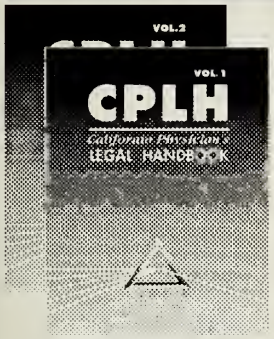

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

June 24-26—**1994 Summer Seminar—Sharing Solutions: Family Practice Pearls & Prevention.** American Academy of Family Physicians at Sheraton Prescott Hotel, Prescott. Fri-Sun. Contact: Ariz AAFP, (602) 249-2021; (800) 933-2237.

July 29-30—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

August 19-20—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

September 10-11—**5th Annual Pulmonary and Infectious Diseases Seminar: September in Sedona.** Mayo Clinic-Scottsdale at Los Abrigados Resort, Sedona. Sat-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

September 25-29—**44th Annual Southwest OB/GYN Meeting.** Southwest OB/GYN Society at Loews Ventana Canyon Resort, Tucson. Sun-Thurs. Contact: Jay Epstein, MD, (602) 678-1111.

October 7-8—**Clinical Assessment in Today's World of Medicine for Nurses.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Scottsdale. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

October 14-15—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

October 21-22—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at Ritz-Carlton Hotel, Phoenix. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

October 28-30—**Arrthymias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Camelback Inn, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

November 4-5—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

November 4-5—**Hematology and Oncology for Primary Care Physicians.** Mayo Clinic-Scottsdale at the Orange Tree Golf Resort, Scottsdale. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 7-11—**The Physician Management Seminar Series: Seminar I.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 7-11—**The Physician Management Seminar Series: Seminar II.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 10-12—**7th Annual Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 17-19—**Pediatric Orthopaedics: A Comprehensive Course.** American Academy of Orthopaedic Surgeons at The Pointe Hilton Resort at Squaw Peak, Phoenix. Thurs-Sat. Contact: AAOS, (708) 823-7186.

December 2-3—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

December 2-4—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Hyatt Regency, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

CARDIOLOGY

July 22-24—**Coronary Heart Disease.** American College of Emergency Physicians at Marriott Tenaya, Yosemite. Fri-Sun. 11 hrs. Contact: Karen DeBont, Meetings Coordinator, 1500 W Canal Ct, Ste #500, Littleton, CO 80120-4528. (800) 421-3756.

July 24-28—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 19 hrs. Contact: UCD.

August 4-6—**Critical Care Cardiology.** American College of Cardiology at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 17 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

September 10—**Primary Care Issues in Cardiac and Vascular Disease.** Alta Bates Medical Center at Claremont Resort, Berkeley. Sat. Contact: Caroline Carey, Alta Bates Med Ctr, (510) 204-3884.

September 23-24—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Desert Inn, Las Vegas, NV. Fri-Sat. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

November 18-20—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

DERMATOLOGY

July 19-23—**11th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD and Scripps Clinic at La Jolla. Tues-Sat. 33 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037 (619) 554-8556.

August 8-10—**Dermatology for the Non-Dermatologists.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 28-31—**Advanced Seminars in Dermatology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Wed. Contact: UCD.

EMERGENCY MEDICINE

June 17-20—**BLS Instructor Course.** CPR Seminars at San Leandro. Fri-Mon. $100. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

June 20-24—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 21-22—**5th Annual High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at Pan Pacific Hotel, San Francisco. Tues-Wed. 15 hrs. $450-$495. Contact: Alpen Travel and Meeting, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 451-RISK (7475).

(Continued on Page 517)

(Continued from Page 516)

July 19-20—**5th Annual High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at Pan Pacific Hotel, San Francisco. Tues-Wed. 15 hrs. $450-$495. Contact: Alpen Travel and Meeting, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 451-RISK (7475).

July 29—**ACLS Recertification.** CPR Seminars at San Francisco. Fri. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

August 15-19—**Emergency Medicine Symposium II.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

September 16—**Advanced Burn Life Support Course.** Torrance Memorial Burn Center at Torrance Memorial Hospital. Fri. 9 hrs. $220. Contact: Nancy Wise, (310) 517-4605.

September 17—**ACLS Recertification.** CPR Seminars at San Francisco. Fri. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

October 14-16—**Advances in Emergency Medicine.** Continuing Medical Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 17-21—**Emergency Medicine Symposium.** UCSD at San Diego Hilton. Mon-Fri. 17 hrs. $475. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

June 23-26—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 18 hrs. $370. Contact: UCLA.

July 5-7—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Tues-Thurs. 20 hrs. $350. Contact: UCSF.

August 5-7—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 19-21—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 19-21—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien, San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

October 7-8—**Coming of Age: Geriatrics for the Primary Care Provider—Part II.** UCD at Sacramento Inn. Fri-Sat. 13 hrs. $235. Contact: UCD.

1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

INTERNAL MEDICINE

June 17-19—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. 12 hrs. Contact: Karen Debont, 1500 W Canal Crt, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 20-24—**Advances in Internal Medicine.** UCSF at Cole Hall, UCSF Campus. Mon-Fri. 33 hrs. Contact: UCSF.

July 9-16—**3rd National Kaiser Permanente Internal Medicine Conference.** Permanente Medical Group at Ritz-Carlton Hotel, Kapalua, Maui, Hawaii. 1 wk. 22 hrs. Contact: Eric Tepper, MD, 3400 Delta Fair Blvd, Antioch 94509. (510) 779-5211.

August 14-19—**11th Annual New Advances in Internal Medicine.** UCD at Hyatt Monterey. Sun-Fri. Contact: UCD.

August 26-September 1—**Comprehensive Nephrology Review Course.** UCLA School of Medicine at Beverly Hilton Hotel, Beverly Hills. Fri-Thurs. 51 hrs. $895. Contact: UCLA.

(Continued on Page 520)

University of Colorado's

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1994 SUMMER/FALL/WINTER SERIES HIGHLIGHTS

JUNE 1994

1. 40th Annual Family Practice Review
   June 12-18, 1994 Estes Park, CO
2. 7th World Conference on Lung Cancer
   June 26-July 1, 1994 Colorado Springs, CO

JULY 1994

3. Integrative Care of Head and Neck Cancer Patients
   July 1, 1994 Denver, CO
4. Treating the Hypoxic Patient
   July 5-9, 1994 Snowmass, CO
5. 30th Annual Internal Medicine Program
   July 10-15, 1994 Estes Park, CO
6. 21st Annual Renal Disease Program
   July 25-29, 1994 Aspen, CO
7. Cardiovascular Intervention: Technology at the Summit, IV
   July 21-August 3, 1994 Aspen, CO
8. 3rd Biannual Type I Diabetes Program
   July 31-August 3, 1994 Keystone, CO

AUGUST 1994

9. 18th Annual Dynamic Psychotherapy Program
   August 1-5, 1994 Aspen, CO
10. 37th Annual Pediatric Program
    August 7-11, 1994 Aspen, CO
11. 19th Annual Primary Musculoskeletal Care
    August 7-12, 1994 Breckenridge, CO
12. The Failing Pediatric Heart
    August 11-14, 1994 Aspen, CO
13. Breast Imaging and Intervention
    August 15-19, 1994 Colorado Springs, CO
14. 4th Annual Musculoskeletal Infection Course
    August 18-20, 1994 Snowmass, CO

SEPTEMBER 1994

15. The Changing Colors of Outreach Education
    September 16-18, 1994 Durango, CO
16. 3rd Annual Medical Ethics Conference
    September 16-18, 1994 Aspen, CO
17. Rocky Mountain Regional Cardiovascular Disease Conference
    September 30, 1994 Vail, CO

NOVEMBER 1994

18. 40th Annual Family Practice Review
    November 7-11, 1994 Denver, CO

DECEMBER 1994

19. Bugs and Drugs
    December 9-10, 1994 Denver, CO

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CORRESPONDENCE

581 **HIV Infection in Women**
LALEKAN A. ARABA-OWOYELE, DVM, MPVM; MICHAEL J. HUGHES, MS; and GEORGE W. RUTHERFORD, MD

582 **Requiem for Medicine?**
JOHN P. BARBUTO, MD
D. GORDON JOHNSTON, MD, Responds

583 **Financing Long-term Care**
JAY B. HANN III, MD
THOMAS BODENHEIMER, MD, Responds

583 **Saccharin Revisited**
CLIFFORD I. CHAPPEL, DVM, PhD
HOWARD H. FRANKEL, MD, PhD, Responds

585 **Using the FAX**
WILLIAM BOWIE, MD

LESSONS FROM THE PRACTICE

586 **The Gift**
KAY F. McFARLAND, MD
From the Department of Medicine, University of South Carolina School of Medicine, Columbia.

587 **Hot Apple Pie for Emma**
BERNARD L. TUCKER, MD
From the Department of Thoracic and Cardiovascular Surgery, Hospital of the Good Samaritan, Los Angeles, California.

OTHER FEATURES

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513 **In Memoriam**

516 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington**

526 **Idaho Medical Association Annual Meeting**

588 **Volume Index**

596 **Instructions for Authors**

598 **Classified Advertising**

608 **Western State Medical Associations' Meetings**

Poems: 561, 575

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

JUNE 23-25, 1994

SOUTHERN ASSOCIATION FOR FAMILY PRACTICE
LOCATION: Williamsburg, VA
SPECIALTY: Family Medicine, Primary Care
CME CREDIT: AMA Category 1
FEE: TBA

JULY 18-21, 1994

FOCUS ON THE FEMALE PATIENT
LOCATION: Kiawah Island Resort, SC
SPECIALTY: OB/Gyn, Primary Care
CME CREDIT: AMA Category 1
FEE: SMA Members $350; Non-Members $475; Non-Physicians $225

JULY 22-24, 1994

FOCUS ON THE MALE PATIENT
LOCATION: Kiawah Island Resort, SC
SPECIALTY: Primary Care
CME CREDIT: AMA Category 1
FEE: SMA Member $310; Non-member $435; Non-Physician $225

JULY 24-27, 1994

GENERAL SURGERY
LOCATION: Sea Island, Georgia
SPECIALTY: Surgery
CME CREDIT: AMA Category 1
FEE: SMA Member $475; Non-member $600; Non-Physician $300

JULY 28-30, 1994

SOUTHERN ASSOCIATION FOR ONCOLOGY ANNUAL MEETING
LOCATION: Jekyll Island, Georgia
SPECIALTY: Oncology
CME CREDIT: AMA Category 1
FEE: SAO Member $400; Non-member $550

JULY 29-31, 1994

PEDIATRICS AND ADOLESCENT MEDICINE
LOCATION: Sea Island, Georgia
SPECIALTY: Primary Care
CME CREDIT: AMA Category 1 - 15 hours
AAFP Prescribed - 15 hours
AOA Category 2-A - 15 hours
FEE: SMA Member $310; Non-member $435; Non-Physician $225

AUGUST 12-14, 1994

MUSCULOSKELETAL PROBLEMS IN PRIMARY CARE
LOCATION: Naples, Florida
SPECIALTY: Primary Care
CME CREDIT: AMA Category 1
FEE: SMA Member $295; Non-member $420; Non-Physician $200

AUGUST 19-21, 1994

SOUTHERN ORTHOPAEDIC ASSOCIATION ANNUAL MEETING
LOCATION: Bermuda
SPECIALTY: Orthopaedic and Traumatic Surgery
CME CREDIT: AMA Category 1
FEE: SOA Member $400; Non-member $550

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!

(Continued from Page 517)

September 17-19—**1994 International Symposium on Bone Marrow Transplantation.** Sutter Community Hospital at Fairmont Hotel, San Francisco. Sat-Mon. Contact: Sutter Community, 2800 L St, Sacramento 95816. (800) 777-0231.

October 22—**Diabetes.** Sutter Community Hospitals at Sacramento. Sat. Contact: Peggy Coit, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

OB/GYN

October 1—**Colscopy.** Sutter Community Hospitals at Sacramento. Sat. Contacat: Lynne MacRae, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

October 1-2—**6th Annual Ultrasound Update: 1994.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $240. Contact: UCD.

October 8—**Women's Health.** Sutter Community Hospitals at Stockton. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

OCCUPATIONAL/ENVIRONMENTAL

July 25-29—**8th Annual Sports Medicine.** UCSD at San Diego Princess Resort. Mon-Fri. 20 hrs. $395. Contact: UCSD.

ONCOLOGY

June 18—**Cancer.** Sutter Community Hospital at Sacramento. Sat. Contact: Sutter Community, 2800 L St, Sacramento 95816. (800) 777-0231.

July 19-22—**Pan Pacific Lymphoma Conference.** University of Nebraska Medical Center at Ritz-Carlton-Mauna Lani, Kohala Coast, Hawaii. Tues-Fri. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

ORTHOPEDICS

July 15-16—**Hand Review 1994.** UCD at Holiday Inn, Capitol Plaza, Sacramento. Fri-Sat. $275. Contact: UCD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

July 23-30—**Update in Orthopaedics '94.** Kaiser Permanente Medical Center, South San Francisco at Hyatt Regency, Maui, Hawaii. Sat-Sat. 18 hrs. $425. Contact: Jerry VanMeter, MD, 1200 El Camino Real, So San Francisco 94080. (415) 742-2461.

August 13-17—**58th Annual Meeting Western Orthopedic Association at Long Beach.** Sat-Wed. 18 hrs. Contact: H. J. Martin, (510) 671-2164.

1994—**Educational Program for Musculoskeletal Evaluation and Rehabilitation.** UCSD at La Jolla. 35.5 hrs. $500. Contact: UCSD.

OTOLARYNGOLOGY

June 5-10 & September 11-16—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

PATHOLOGY

August 13-20—**15th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton Mauni Lani, Big Island of Hawaii. Sat-Sat. 27 hrs. $950. Contact: UCSF.

August 24-27—**Centennial Conference on Coccidioidomycosis.** Stanford University at University Campus. Wed-Sat. Contact: Complete Conference Management, 1660 Hotel Circle North, #220, San Diego 92108. (619) 299-6673.

September 17—**34th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott. Sat. Contact: National Kidney Foundation, 5777 W. Century Blvd, Ste 395, Los Angeles 90045-7404. (310) 641-8152.

September 17-21—**9th Combined Skin Pathology Course and 5th Annual Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sat-Wed. 40 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

June 24-26—**Current Concepts in Child Neurology 1994.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15 hrs. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

July 15-17—**2nd Annual Pediatric Update.** Stanford University School of Medicine at Lucile Packard Children's Hospital, Palo Alto. Fri-Sun. Contact: Elinor Meyer, Medical Outreach Dept, 725 Welch Rd, Palo Alto 94304. (415) 497-8554.

August 22-24—**Pediatrics Update 1994.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 1—**Therapy for Childhood Neuromuscular Diseases.** Children's Hospital and Health Center at Hyatt Regency, San Diego. Sat. 6.5 hrs. $75. Contact: CAM, 3030 Children's Way, San Diego 92123. (619) 576-5819.

October 22—**Pediatrics.** Sutter Community Hospitals at Auburn. Sat. Contact: Lynne MacRae, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

October 29—**Ambulatory Pediatrics.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

PHYSICAL MEDICINE/REHABILITATION

August 11-13—**2nd Annual Clinical Exercise, Physiology and Cardiac Rehabilitation Conference.** American College of Cardiology at Holiday Inn, Palo Alto. Thurs-Sat. 21 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

October 8-12—**56th Annual Assembly, American Academy of Physical Medicine and Rehabilitation** at Anaheim Hilton Hotel and Towers and Anaheim Convention Center. Sun-Wed. Contact: AAPMR, 122 S Michigan Ave, Ste 1300, Chicago, IL 60603-6107. (312) 922-9366.

PSYCHIATRY

June 24-26—**Eating Disorders: A Clinical Update.** Continuing Medical Education Incorporated at Anaheim Hilton Hotel and Towers. Fri-Sun. 17 hrs. $495. Contact: CME Inc, 1924 E Deere Ave, Santa Ana 92705-5723. (800) 447-4474; (714) 250-1008.

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THE WESTERN JOURNAL OF MEDICINE'S 1994 SPECIAL ISSUE

NEUROLOGY—
FROM BASICS TO BEDSIDE

Stephen L. Hauser, MD, Special Issue Editor

DECADE OF THE BRAIN–
AN AGENDA FOR THE
NINETIES
Murray Goldstein, MD
NIH

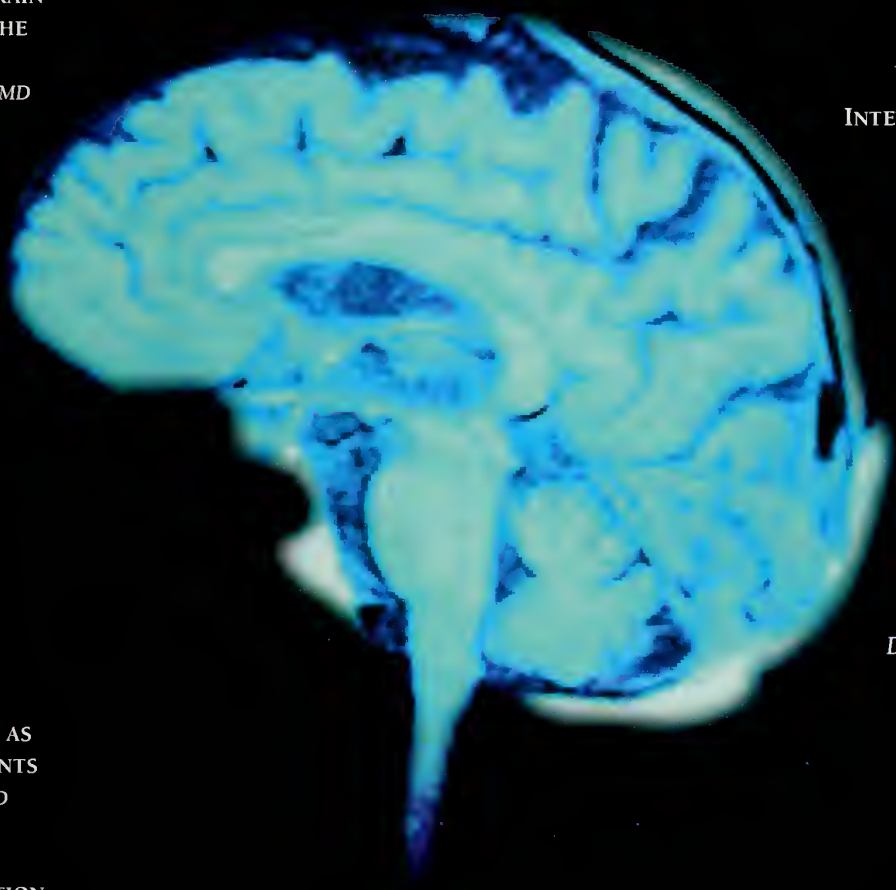
NEUROGENETICS–
TRIUMPHS AND
CHALLENGES
Thomas Bird, MD
University of Washington

MAPPING BRAIN
ACTIVITY IN VIVO
John Mazziota, MD
UCLA

THE BIOLOGY OF
ADDICTION
Ivan Diamond, MD
UCSF

GROWTH FACTORS AS
THERAPEUTIC AGENTS
William Mobley, MD
UCSF

NEUROREHABILITATION
Fletcher McDowell, MD
Cornell University Medical School



NEUROIMAGING
Robert Ackerman, MD
Mass General Hospital

INTENSIVE CARE UROLOGY
Jeffrey Frank, MD
Cleveland Clinic

PRIONS
Stanley Prusiner, MD
UCSF

GENE THERAPY
Mark Israel, MD
UCSF

NEURO-
THERAPEUTICS:

MULTIPLE SCLEROSIS
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(Continued from Page 520)

June 28-July 3—**Neuropsychiatric Aspects of Aging: Update and Review.** Southern California Neuropsychiatric Institute at Mauna Kea Hotel, Hawaii. Tues-Sun. 22 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

October 7-11—**The Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Colonial Inn, La Jolla. Fri-Tues. 26 hrs. Contact: UCSD.

October 14-15—**Psychopharmacology Clinical Research Update.** UCD at Hilton Hotel, San Francisco. Fri-Sat. 14 hrs. $395. Contact: UCD.

1994—**Basic Clinical Hypnosis Training.** UCSD at La Jolla. Ongoing. 30 hrs. $245. Contact: UCSD.

PULMONARY MEDICINE

August 12-14—**Diagnosis and Management of Respiratory Diseases.** American College of Emergency Physicians at Hyatt Regency, Lake Tahoe, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

September 23-25—**Diagnosis and Management of Respiratory Diseases.** American College of Emergency Physicians at Esmeralda Resort, Palm Springs. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

RADIOLOGY

August 25-28—**Physics of Diagnostic Radiology.** UCD on Campus. Thurs-Sun. Contact: UCD.

October 10-14—**Neuroimaging Visiting Fellowship Program.** Stanford School of Medicine. Mon-Fri. 40 hrs. Contact: Barbara Platt. (415) 723-4733.

October 17-19—**Radiology for the Non-Radiologist.** UCSD at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $450. Contact: UCSD.

1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

1994—**Visiting Fellowship Program of Endovaginal Sonography: Focus on Techniques and Application.** UCSD Medical Center. Monthly. 30 hrs. $600. Contact: UCSD.

SURGERY

June 23-25—**20th Annual Meeting of the Western Thoracic Surgical Association.** WTSA at Resort at Squaw Creek, Olympic Valley. Thurs-Sat. Contact: WTSA, (508) 526-8330.

September 9-13—**Summer Institute—Intensive Surgical Skills.** American Academy of Orthopedic Surgeons at Monterey Conference Center, Marriott Hotel and Doubletree Hotel, Monterey. Fri-Tues. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

October 29—**Suture Workshop.** Sutter Community Hospitals at Sacramento. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

GENERAL/MULTIDISCIPLINARY

July 14-15—**New Approaches to Define Nutrient Requirements.** UCD at Western Human Nutrition Research Center, San Francisco. Thurs-Fri. 13 hrs. $125. Contact: UCD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

July 8-10—**Common Problems in Primary Care.** P/SL Swedish Healthcare System at Snowmass. Fri-Sun. Contact: Nancy Manuel, (303) 788-6209.

July 8-10—**Current Concepts in Heart Failure: Medical Treatment to Mechanical Support and Transplantation.** P/SL Swedish Healthcare System at Snowmass. Fri-Sun. Contact: Nancy Manuel, (303) 788-6209 or P/SL CME Office, (800) 633-6824.

July 10-15—**30th Annual Internal Medicine Program.** University of Colorado Health Sciences Center at YMCA of the Rockies, Estes Park. Sun-Fri. Contact: U of Colo.

July 25-29—**21st Annual Renal Disease Program: Renal Disease and Electrolyte Disorders.** University of Colorado Health Sciences Center at The Given Biomedical Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 31-August 3—**Third Biannual Type 1 Diabetes Program: Management of Pediatric Diabetes.** University of Colorado Health Sciences Center at Keystone. Sun-Wed. Contact: U of Colo.

July 31-August 3—**Cardiovascular Interventions: Technology at the Summit, IV.** University of Colorado Health Sciences Center at Aspen. Sun-Wed. Contact: U of Colo.

August 1-5—**Dynamic Psychotherapy Program.** University of Colorado Health Sciences Center at Aspen. Mon-Fri. Contact: U of Colo.

August 7-11—**37th Annual Pediatric Program.** Children's Hospital and University of Colorado Health Sciences Center at The Given Biomedical Institute, Aspen. Sun-Thurs. Contact: U of Colo.

August 7-12—**19th Annual Primary Musculoskeletal Care Program.** University of Colorado Health Sciences Center at Breckenridge. Sun-Fri. Contact: U of Colo.

August 8-12—**12th Annual Pediatric Infectious Disease Conference.** Children's Hospital at Aspen. Mon-Fri. Contact: Kim Brenckle, Children's Hospital, 1056 E 19th Ave, Box 055, Denver. (303) 861-6981.

August 11-13—**Pediatric Cardiology: The Failing Heart.** University of Colorado School of Medicine at The Given Biomedical Institute, Aspen. Wed-Sat. Contact: U of Colo.

August 11-14—**Fourth Annual Conference: Women Physicians/Finding a Balance.** Rose Medical Center at Breckenridge Hilton Hotel. Thurs-Sun. Contact: Women Physicians Conference, 9101 E Kenyon Ave, #3000, Denver 80237. (303) 770-2220; FAX (303) 770-1812.

August 11-14—**Multimodality Approaches to Limb Salvage for Extremity Sarcoma.** P/SL Swedish Healthcare System at Westin Resort, Vail. Thurs-Sun. Contact: P/SL CME Office, (800) 633-6824.

August 14-17—**Fourth National Kaiser Permanente Emergency Medicine Conference.** Colorado Medical Society and Colorado Permanente Medical Group at Beavercreek. Contact: KPEM 94, PO Box 7131, Corte Madera, CA 94976-7131. (415) 927-7450.

August 15-20—**Breast Imaging and Intervention Into the 21st Century.** Radiology Imaging Associates at Broadmoor Hotel, Colorado Springs. Sun-Fri. Contact: Ryals & Associates, (404) 641-9773.

August 17-19—**Genetic Therapy.** University of Colorado Health Sciences Center at Aspen. Wed-Sat. Contact: U of Colo.

August 17-20—**4th Annual Musculoskeletal Infection Meeting.** University of Colorado Health Sciences Center at Snowmass Village. Wed-Sun. Contact: U of Colo.

September 16-18—**Sixth National Conference on Outreach Education: The Changing Colors of Outreach Education.** University of Colorado Health Sciences Center at Tamarron Resort, Durango. Fri-Sun. Contact: U of Colo.

September 16-18—**Third Annual Medical Ethics Conference.** University of Colorado Health Sciences Center at Aspen. Fri-Sun. Contact: U of Colo.

September 30—**Rocky Mountain Regional Cardiovascular Disease Conference.** University of Colorado Health Sciences Center at Vail. Fri. Contact: U of Colo.

(Continued on Page 523)

CONTINUING MEDICAL EDUCATION

(Continued from Page 522)

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

Every Friday (except 4th Friday of month)—**Various Topics in Contemporary Medicine (Midday CME Series).** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

July 28-30—**Idaho Medical Association—Annual Meeting.** Sun Valley. Wed-Fri. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

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Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

June 30-July 3—**Highlights in Women's Health Care.** Hotel Santa Fe. Thurs-Sun. 17 hrs. Contact: Ada Brandemuehl, Scott & White Hospital, 2401 S 31st St, Temple, TX 76508. (817) 724-2350.

July 14-17—**Sports Medicine and Imaging.** The Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 18-22—**Imaging 1994.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 22-24—**Arrhythmias, Diagnosis and Treatment.** Eldorado Hotel, Santa Fe. Fri-Sun. Contact: Tracy L. Green, New Mexico Heart Clinic, (505) 841-1000.

August 7-11—**Lovelace Santa Fe Neurology 1994.** Eldorado Hotel, Santa Fe. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 16-17—**Annual Meeting—American College of Surgeons, New Mexico Chapter.** Hotel de Santa Fe, Santa Fe. Contact: Bonnie Smith, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237.

September 17—**Management of Patient with Cardiac Disease.** Journal Center, Albuquerque. Sat. Contact: Tracy L. Green, New Mexico Heart Clinic, (505) 841-1000.

October 5-9—**3rd Annual New Mexico Medical Computer Course.** Holiday Inn Pyramid Hotel, Albuquerque. Contact: Floyd Smith, NMOMA, PO Box 90396, Albuquerque 87199-0396. (505) 828-1905.

October 28-29—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sun. Contact: Tracy L. Green, New Mexico Heart Clinic, (505) 841-1000.

(Continued on Page 597)

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The patient subsequently was bone grafted by Dr. Patzakis due to a 2-inch bone defect and nonunion. At six months, the patient's fracture was healed and he was ambulating. He returned to work 10½ months after undergoing vocational rehabilitation and remains infection free with an excellent functional result.

Michael J. Patzakis, M.D., professor and chairman of Orthopaedics at the USC School of Medicine and director of the USC Orthopaedic Infection Service has arrested infection in many of his patients with chronic osteomyelitis using several new treatment modalities.

Dr. Patzakis joined the USC School of Medicine faculty in 1969 after holding an academic post at the University of Colorado, where he previously completed his fellowship in rheumatoid surgery. He earned his medical degree from Ohio State University, and completed his orthopaedic residency at Los Angeles County+USC Medical Center. He is a member of numerous professional organizations, and in 1991 served as president-elect of the International Muscular Skeletal Infection Society.

The Center's multidisciplinary team, faculty of the USC School of Medicine is recognized for its clinical expertise in the treatment of osteomyelitis, infected non-unions of bones, infected total joints, bone reconstruction and muscle and microvascular soft tissue transfers. The team is led by Dr. Patzakis, who has earned an international reputation for his clinical expertise in orthopaedic infections, osteomyelitis and septic arthritis. He specializes in the treatment of orthopaedic infections, in association with Randy Sherman, M.D., who specializes in plastic and microvascular surgery; and, Jackson Lee, M.D., whose specialty is orthopaedic trauma.

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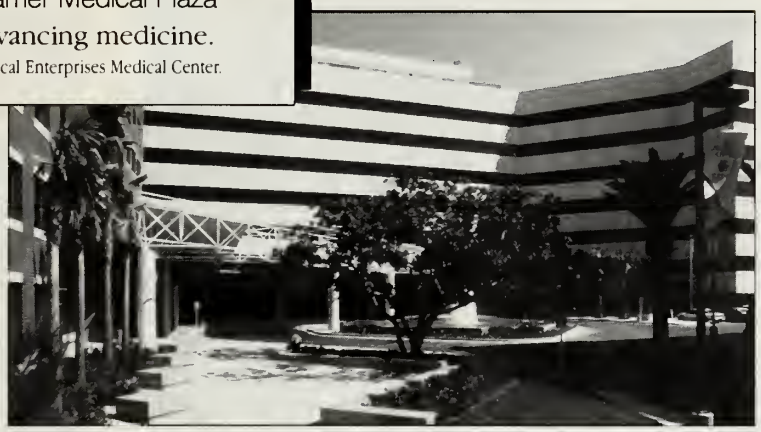

Because of treatments including more potent antibiotics and aggressive surgical approaches such as bone grafting, soft tissue transfers and revascularization techniques, it is now possible to achieve arrest in many infections that previously led to amputations or were considered incurable.

The beads shown above resemble a string of pearls, but in fact are actually antibiotic-impregnated beads — a new weapon in the ongoing fight against bone infection. The chain of antibiotic beads are surgically placed within the area of the infected bone or joint, allowing the antibiotic to leach out into the surrounding tissues.

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SCIENTIFIC SESSION

Friday, July 29, 1994

7:30 am	TECHNICAL EXHIBITS OPEN CONTINENTAL BREAKFAST
8:15 am	WELCOME—Daniel Miller, MD, Idaho Medical Assoc. President
8:30-9:30 am	MOLECULAR BIOLOGY IN CLINIC PRACTICE—A PRIMER OF TECH AND PRACTICE Malcolm Winter, MD
9:30 am	RECESS TO VIEW EXHIBITS
10:00- 11:00 am	UPDATE ON CARDIOVASCULAR SURGERY Timothy Icenogle, MD
11:00-noon	DRUG EFFICACY AND COST-CUI CONTROVERSY AND SOLUTION Richard E. Bryant, MD
12:00- 1:30 pm	ALLIANCE LUNCHEON (Spouses Welcome) ADDING LAUGHTER TO OUR LIV Speaker: Marilyn Grey
1:30-2:30 pm	VIOLENCE IN AMERICA, THE NA TRUE HEALTH CARE CRISIS Allan Hoffman, EdD
2:30-3:30 pm	THE FUTURE ISN'T WHAT IT USI BE—HMO'S, THE PROFESSION' RESPONSE Howard Lang, MD

Saturday, July 30, 1994

10:00 am	Richard Kennedy, MD, President Canadian Medical Association

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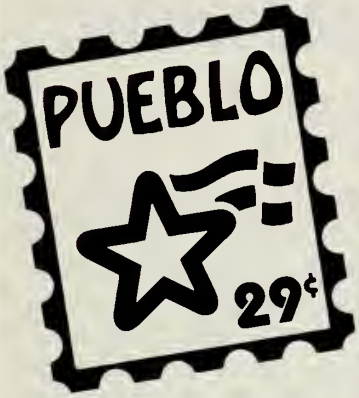

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See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or *PDR*. The following is a brief summary.

Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below

Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Sinusitis caused by β-lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus, E. coli*, and *Klebsiella* spp

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli, Klebsiella* spp and *Enterobacter* spp

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate

Contraindications: A history of allergic reactions to any penicillin is a contraindication

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is 1 primary cause of "antibiotic associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy

A high percentage of patients with mononucleosis who received ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently

Augmentin should not be co-administered with Antabuse® (disulfiram)

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%)

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache

The following adverse reactions have been reported for ampicillin class antibiotics

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS)

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely

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* For susceptible strains of indicated organisms. *Augmentin* is appropriate initial therapy when you suspect ß-lactamase-producing organisms.

† Latest available annual data: January to December 1991.

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

References: 1. Neu HC, Wilson APR, Grüneberg RN Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5(2):67-93. **2.** Data on file, SmithKline Beecham Pharmaceuticals. **3.** Data from the Institutes for Microbiology Research, Franklin, Tenn. **4.** Neu HC: Contribution of beta-lactamases to bacterial resistance and mechanisms to inhibit beta-lactamases. *Am J Med* 1985;79(suppl 5B):2-12.

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Articles

Management of Upper Respiratory Tract Infections by Telephone

STEVE JEPSON, MD; JOHN H. HOLBROOK, MD; DeVON HALE, MD; *and*
JOSEPH LYON, MD, *Salt Lake City, Utah*

We surveyed Utah general internists (N = 134) regarding their attitudes toward and practices associated with telephone management of upper respiratory tract infections. The questionnaire contained 3 case vignettes—viral upper respiratory tract infection, streptococcal pharyngitis, and acute infectious epiglottitis—and a series of questions were asked about telephone diagnosis, management preferences (clinic versus telephone), and telephone management practices. The 53 respondents (40%) were able to make important diagnostic distinctions about upper respiratory tract infections from a written vignette. As the likelihood of a complicated or serious condition increased, patients would be appropriately triaged for clinical evaluation. Most internists would make a written record of the telephone conversation. Only 1 internist of the 53 would charge for telephone management.

(Jepson S, Holbrook JH, Hale D, Lyon J: Management of upper respiratory tract infections by telephone. West J Med 1994; 160:529-533)

The telephone has become an essential tool in contemporary patient-physician communication. In fact, telephone calls account for about 25% of all patient encounters in the practice of general internal medicine.[1,2] Recent studies cataloguing the types of telephone calls made to internists show that 45% of calls are symptom-related and that nearly half of these problems are managed exclusively over the telephone.[3-5] Because internists use the telephone so frequently in disease management, understanding how medicine is practiced on the telephone is important.

Other primary care specialists, such as family practitioners and pediatricians, have given some attention in their literature to the issue of telephone medicine.[6-12] Pediatricians have studied the outcome of cases of telephone-diagnosed otitis media[6] and compared telephone management skills of nurse practitioners, residents, and attending physicians.[7,8] In one study the personal characteristics (of both patient and physician) that lead to office visits instead of telephone management were investigated.[9] In another, the development of telephone management skills through residency training was examined.[10]

General internists have also investigated the telephone as a management tool, but this has been done primarily for chronic disease management. Telephone counseling has been found to be at least as effective as face-to-face visits in helping patients achieve and maintain blood pressure control.[13] Substituting telephone follow-up for selected clinic visits has reduced the use of medical services and may improve patients' health.[14]

Because more than a third of symptom-related telephone calls made to general internists concern acute problems, it is surprising that the telephone management of acute medical problems by internists is not well studied. Our goal, therefore, was to investigate the attitudes toward and practices associated with the telephone management of acute disease by general internists. We chose upper respiratory tract (URI) infection to study because it is the most common acute disease encountered by general internists over the telephone.[3] We focused on the following questions:

- Are internists able to make important diagnostic distinctions about URIs over the telephone?
- How willing are general internists to treat various types of URIs exclusively over the telephone?
- What factors contribute to extending management to the office?
- What kinds of medications are prescribed over the telephone for various types of URI?
- How do internists chart and bill for telephone management?
- What methods of patient follow-up are most commonly used?

Subjects and Methods

We conducted a survey of general internists practicing in the state of Utah, obtaining names and addresses from the Utah Medical Association. The majority (>85%) of surveyed internists practice in the metropolitan area, where 80% of the state's population resides. The rest

From the Division of General Internal Medicine (Drs Holbrook and Hale) and the Department of Family and Preventive Medicine (Dr Lyon), University of Utah School of Medicine, Salt Lake City. At the time this article was written, Dr Jepson was a fourth-year medical student. He is now a resident in internal medicine at Providence Medical Center, Portland, Oregon.

Reprint requests to John H. Holbrook, MD, University Hospital, 4B120, Salt Lake City, UT 84132.

ABBREVIATIONS USED IN TEXT

CI = confidence interval
URI = upper respiratory [tract] infection

practice in rural Utah. We excluded only those internists working for the Family Health Program, Utah's largest health maintenance organization, to avoid biasing our data with one large group's practice of telephone medicine.

We mailed each physician a questionnaire containing three standardized case histories, each involving a different type of acute URI. Physicians were instructed to assume that in each case the caller was a regular clinic patient who had been seen by them on more than one occasion, had no other important medical problems, and was calling during regular office hours in the month of December. These vignettes were designed to represent a self-limited infection: viral URI; an infection with possible long-term complications: streptococcal pharyngitis; and an infection that if not recognized is potentially lethal: acute infectious epiglottitis (Figure 1). The physicians were told to assume that each history was taken over the telephone.

Case A The patient is a 37-year-old woman whose symptoms include malaise, nasal congestion, sneezing, and sore throat for the past 2 days. A nonproductive cough developed this morning. She took her temperature this morning, and it was 37.6°C (99.7°F). She does not have chills, nausea, myalgias, headache, purulent nasal drainage, difficulty breathing, or sinus tenderness and has not had contact with an ill person. She does not see any white coating in the back of her throat and cannot feel any tender nodes. She called because she is feeling a little "sicker" than she usually does when she has a cold.

Case B The patient, a 25-year-old male medical student, just finished working in the pediatric clinic. His symptoms, which developed 2 days ago, include malaise, sore throat, nasal congestion, myalgias, and headache. He does not have a thermometer, but his wife thinks he feels "warm." He does not have dysphagia, cough, chills, nausea, sinus tenderness, or difficulty breathing. He is fairly certain that there is exudate in the back of his throat, and he has some tender lymph nodes in the submandibular area at the angle of the jaw. He would like a prescription for an antibiotic.

Case C The patient, a 42-year-old man, reports a progressive sore throat and hoarseness over the past 2 days, and he is now having difficulty swallowing. It is painful to even swallow secretions, so he frequently spits out the saliva that accumulates in his mouth. His temperature is 38.6°C (101.5°F). He does not have nasal congestion, myalgias, headache, or nausea. He has tried to cough, but it is somewhat painful, and at times he feels a little short of breath. He apologizes for calling, but says that his wife made him do it because she worries too much.

Figure 1.—Case history vignettes were used in the questionnaire sent to general internists to assess telephone management of acute illnesses. Case A represents viral upper respiratory tract infection, case B represents streptococcal pharyngitis, and case C represents acute infectious epiglottitis.

TABLE 1.—*Frequency of Upper Respiratory Tract Infection (URI) Type Given in the Differential Diagnosis*

Disease	*Responses, No. (% of total)**	CI_{95}
Case A		
Viral URI	34 (64)	51, 77
URI	9 (17)	7, 27
Viral syndrome	5 (9)	1, 17
Bronchitis	3 (6)	0, 12
Chlamydia	1 (2)	0, 6
Influenza	1 (2)	0, 6
No diagnosis	1 (2)	0, 6
	54	
Case B		
Streptococcal pharyngitis	40 (75)	63, 87
Unspecified pharyngitis	6 (11)	3, 19
Viral URI	6 (11)	3, 19
URI	5 (9)	1, 17
Mononucleosis	4 (8)	1, 15
Viral pharyngitis	4 (8)	1, 15
Viral syndrome	1 (2)	0, 6
No diagnosis	1 (2)	0, 6
	67	
Case C†		
Acute infectious epiglottitis	19 (36)	23, 49
Unspecified pharyngitis	16 (30)	18, 42
Streptococcal pharyngitis	6 (11)	3, 19
Tonsillitis	6 (11)	3, 19
Peritonsillar abscess	5 (9)	1, 17
Viral URI	5 (9)	1, 17
No diagnosis	3 (6)	0, 12
Retropharyngeal abscess	2 (4)	0, 6
Pneumonia	2 (4)	0, 6
Herpes stomatitis	2 (4)	0, 6
	56	

CI_{95} = 95% confidence interval

*Percentages were figured on number of diagnoses listed and may exceed the number of respondents.

†All of the following were listed once under case C: influenza, tracheitis, laryngotracheitis, viral syndrome, quinsy, bronchitis.

After each vignette, the physicians were asked to give a presumptive diagnosis and then asked whether they would manage the patient's problem over the telephone exclusively or if they would ask the patient to come into the office for an examination. If they chose the telephone management option, they were asked to respond to a series of questions regarding their telephone management practices (Figure 2). If they responded in favor of an

Would you prescribe any of the following medications?

A. antibiotic
B. decongestant
C. cough suppressant

Would this phone call be recorded in the patient's chart?

With prescription Yes _____ No _____
Without prescription Yes _____ No _____

Would you bill the patient for this encounter?

Yes _____ No _____
If yes, how much? _____

How would you follow up this problem?

A. by telephone
B. schedule a clinic visit
C. as needed

Figure 2.—The questions that were asked of general internists regarding telephone management practices are shown.

office visit, we asked them to indicate what additional information they thought was most important to obtain (Figure 3).

Statistical analysis was done by calculating percentages for each respondent. A 95% confidence interval (CI) was also calculated for each percentage. Because this was a descriptive study, we did not do formal hypothesis testing using *P* values. The percentages were determined on the number of diagnoses given, and thus they may exceed the number of respondents, but confidence bounds were calculated based on the number of respondents.

Results

The questionnaires were sent to 134 general internists throughout Utah. A total of 53 completed questionnaires were returned (40%).

Table 1 shows the frequency with which specific types of URI were given as the presumptive diagnosis for each case. Internists arrived at the "correct" presumptive diagnosis, or included it in their differential diagnosis, 64% of the time for case A (viral URI) and 75% of the time for case B (streptococcal pharyngitis). For case C (acute infectious epiglottitis), 19 respondents (36%) provided the correct diagnosis. For case A, only 1 respondent listed more than one diagnosis. For case B, 14 respondents listed a differential diagnosis with two or more possible diagnoses. For case C, 23 respondents listed more than one diagnosis.

TABLE 2.—*Physicians Willing to Telephone Manage Versus Those Wanting an Office Visit*

Case, Diagnosis	Respondents: Telephone Only (n = 53), No. (%)	CI_{95}	Office Visit (n = 53), No. (%)	CI_{95}
A, Viral URI	42 (79)	69, 91	11 (21)	9, 31
B, Streptococcal pharyngitis	17 (32)	19, 45	36 (68)	55, 81
C, Epiglottitis	0 (0)	--	100	--

CI_{95} = 95% confidence interval, URI = upper respiratory [tract] infection

Which *one* of the following best describes your reason for this answer:

A. Not enough information is provided. Please list the additional historical information that you require:
B. Would like to examine this patient.
C. Would like to perform tests. Please list the tests you would order:
D. Other. Please specify:

Figure 3.—The questions that were asked to elicit reasons for wanting to see a patient in the office instead of providing care over the telephone are shown.

As expected, the percentage of physicians willing to treat over the telephone varied by the symptoms given in the case scenario. For case A, 42 (79%; 95% CI, 69% to 91%) were willing to treat over the phone, and only 5 (12%) would use antibiotics (Tables 2 and 3). For case B, only 17 (32%; 95% CI, 19% to 44%) would treat over the phone. For case C, none were willing to treat over the telephone. Thus, no further information about telephone treatment can be gleaned from this case.

Telephone management practice patterns for charting

TABLE 3.—*Telephone Management Practices: Medications Prescribed Over the Telephone, Charting, and Follow-up**

Practice	Respondents: Case A (n = 42), No. (%)	CI_{95}	Case B (n = 17), No. (%)	CI_{95}
Medication Prescribed				
Antibiotic	5 (12)	2, 22	16 (94)	83, 105
Decongestant	30 (71)	57, 85	7 (41)	18, 64
Cough suppressant	17 (40)	25, 55	1 (6)	0, 17
Record in Chart				
With prescription				
Yes	33 (79)	67, 91	13 (76)	56, 96
No	3 (7)	0, 15	3 (18)	0, 36
No response	6 (14)	4, 25	1 (6)	0, 17
Without prescription				
Yes	27 (64)	51, 79	7 (41)	18, 64
No	9 (21)	9, 33	2 (12)	0, 27
No response	6 (14)	4, 25	8 (47)	23, 71
Follow-up Method				
As needed	40 (95)	87, 101	13 (76)	56, 96
Telephone	2 (4)	0, 10	3 (18)	0, 36
Clinic	0 (0)	--	1 (6)	0, 17

CI_{95} = 95% confidence interval

*Case C was not included because 100% of respondents would not manage such a case over the telephone.

TABLE 4.—*Diagnostic Steps Considered Most Important by Respondents Requesting Further Office-Based Workup*

	Respondents					
	Case A (n = 11), No. (%)	CI_{95}	Case B (n = 36), No. (%)	CI_{95}	Case C (n = 53), No. (%)	CI_{95}
Additional history	0 (0)	--	1 (3)	0, 9	5 (9)	1, 17
Physical examination	10 (91)	74, 108	23 (64)	48, 80	43 (81)	70, 91
Laboratory tests	1 (9)	0, 26	22 (61)	45, 77	19 (36)	23, 49

CI_{95} = 95% confidence interval

and follow-up are also detailed in Table 3. Only one respondent indicated that he or she would charge a calling patient for telephone management. For this service the evaluation and management code 99212 was used.

Table 4 shows which additional diagnostic steps were considered most important by those respondents uncomfortable managing these cases based on telephone information alone. Although the questionnaire asked for only one answer to this question, many respondents listed two or more steps (9 respondents for case B and 14 for case C). Table 5 shows which tests were requested by respondents who would be in favor of laboratory testing for cases B and C (only one respondent requested a test for case A—an Abbott Test Pack, Strep A). For case C, five respondents asked for additional information concerning nausea and vomiting, "ill contacts," recent use of antibiotics, immunization history, and a review of systems.

Discussion

Infectious pharyngitis is the most common cause of a sore throat. Common etiologic agents include *Streptococcus, Chlamydia,* and *Mycoplasma* species and Epstein-Barr virus and other viruses such as adenovirus. The differential diagnosis should also include rare causes of infectious pharyngitis, disorders with referral of pain to the throat, and systemic illnesses.

Based on telephone information alone, our respondents made the "correct" presumptive diagnosis on the more common disorders, viral URI and streptococcal pharyngitis. Case C, which represented a less common but potentially more dangerous URI, was much more difficult for the respondents to diagnose based on the telephone information alone. A total of 14 different diseases were given as possible diagnoses. Although only 19 (36%) of the respondents gave the "correct" presumptive diagnosis, acute infectious epiglottitis, all recognized the seriousness of the problem and indicated they would want to see the patient.

Most of our respondents (80%) were willing to manage the case representing a viral URI over the telephone. Of these 42 physicians, 5 (12%) prescribed an antibiotic; a decongestant was the most commonly prescribed medication for this case. The low percentage of physicians prescribing antibiotics for presumed URIs may not reflect the actual practice of clinicians in the community. A prospective study of clinician behavior would be necessary to define actual practice patterns. Among the 11 respondents who wanted to see the patient with the viral URI in their office (21%), all but one listed the physical examination as the most important reason for an office visit.

Fewer respondents (17, or 32%) were willing to manage the case representing streptococcal pharyngitis over the telephone. Those who did choose telephone management prescribed an antibiotic in all but one instance. Those who preferred office management (36, or 68%) mentioned the physical examination and laboratory testing with nearly equal frequency as the most important reason for an office visit.

No respondent was willing to manage the case representing acute infectious epiglottitis over the telephone. The physical examination was the most frequently given reason for having patient C come into the office. It has been hypothesized that the probability of a physician asking a calling patient to come to the office decreases with the certainty of the diagnosis. It has also been suggested that the probability of a physician asking a patient to come to the office increases with the perceived seriousness of the illness. Our findings support these interpretations.

In our view the patient in case A could be appropriately managed over the telephone with symptomatic treatment, supportive care, and appropriate follow-up. Antibiotics should not be given in this case because of their ineffectiveness, expense, and the potential for adverse reactions.

The appropriate management of case B is complex.

TABLE 5.—*Specific Laboratory Tests Requested by Respondents Wanting Office Management Who Listed Laboratory Testing as the Most Important Diagnostic Step*

Test	Respondents No.	(% of total)	CI_{95}
Case B (n = 22)			
Throat culture	12	(55)	34, 76
Streptococcal A	12	(55)	34, 76
Monospot*	6	(26)	8, 44
CBC with differential WBC	4	(17)	1, 33
Case C (n = 19)			
Throat culture	9	(47)	24, 69
Neck x-ray films, AP and lateral	8	(42)	20, 64
CBC with differential WBC	6	(32)	11, 53
Streptococcal A	5	(26)	6, 46
Monospot*	3	(16)	0, 33
Chest x-ray film	2	(11)	0, 25

AP = anteroposterior, CBC = complete blood count, CI_{95} = 95% confidence interval, WBC = white blood count

*Monospot slide test for infectious mononucleosis.

The major role of the clinician in this case is to identify correctly and treat group A streptococcal infection. Because the patient has a high likelihood of having such an infection, treatment with an antibiotic prescribed over the telephone may be the correct decision. In most such cases, however, the issues are far less clear, and the patient should be examined. Because the diagnosis of group A streptococcal infection cannot be made on clinical grounds, evaluation with serologic testing, throat culture, or both is usually indicated.

The appropriate management of the patient in case C consists of recognizing the severity of the problem, suspecting the diagnosis, and arranging for immediate clinical evaluation. In this case, visualization of the epiglottis by laryngoscopy is indicated.

Depending on the case and the treatment, between 41% and 79% (7 to 33) of the internists would make a written record of the telephone conversation. Most of them follow up on telephone management on an as-needed basis only. In our view, most physician-patient interactions, including those conducted over the telephone, should be recorded in a patient's chart.

The overwhelming majority of responding internists do not charge for telephone management. In a time when generalists' incomes are relatively low, not charging for this time-consuming activity is an economic anomaly. This is an area where additional study is needed to identify national trends and to define the issues determining whether telephone management should be a billed service.

This survey is limited because it did not include demographic data about the respondents. Also, the vignettes were so "classical" that many diagnostic vagaries were avoided, and the questionnaire format eliminated certain real-world pressures of medical practice. Although the results may not reflect actual practice patterns, they provide descriptive data in an important clinical area that has received little scientific scrutiny.

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Articles

Lyme Disease in Northwestern Coastal California

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To determine the incidence of physician-diagnosed Lyme disease in an endemic area of California, an active surveillance program was implemented in Lake, Mendocino, Sonoma, and southern Humboldt counties. More than 200 medical care providers were called monthly for their list of suspected cases of Lyme disease. Pertinent information was abstracted from the medical record of each patient.

Of 153 cases of possible early Lyme disease ascertained from July 1991 to December 1992, 37% consisted of physician-diagnosed erythema migrans. Only 58% of erythema migrans rashes were at least 5 cm in diameter. An additional 43 patients had suspicious rashes not classified as erythema migrans. Of 166 patients with possible late-stage Lyme disease, 31% had specific clinical symptoms and 75% had a positive serologic test.

With an incident case defined as physician-diagnosed erythema migrans of at least 5 cm in diameter, the annual incidence of Lyme disease in northwestern coastal California according to active surveillance only was 5.5 per 100,000. The rate of Lyme disease in California is substantially lower than that in the Atlantic northeastern United States. Many suspected cases of Lyme disease in this endemic area do not meet surveillance criteria, which are intentionally restrictive. Although some of the illnesses not meeting surveillance criteria may be due to infection with *Borrelia burgdorferi*, it appears that Lyme disease is being overdiagnosed in this area.

(Ley C, Davila IH, Mayer NM, Murray RA, Rutherford GW, Reingold AL: Lyme disease in northwestern coastal California. West J Med 1994; 160:534-539)

Borrelia burgdorferi causes Lyme disease, a multisystem illness with dermatologic, musculoskeletal, neurologic, or cardiac manifestations.[1-3] In the Pacific northwestern United States, this spirochete is transmitted by the western black-legged tick, *Ixodes pacificus*; an average of 1% to 2% of these ticks are infected in northern California.[4]

Difficult to grow in culture from humans and requiring special media,[5] *B burgdorferi* has been identified in only three patients in California to date (G. L. Campbell, MD, PhD, MPH, Centers for Disease Control and Prevention, Fort Collins, Colorado, oral communication, August 1993). Furthermore, because the available serologic tests for antibodies to *B burgdorferi* are not standardized, vary widely in sensitivity and specificity, and typically give negative results early in the course of infection, they are not useful as diagnostic tools.[6-8] Thus, Lyme disease remains a clinical diagnosis. Unfortunately, many of the signs and symptoms associated with Lyme disease are nonspecific, and there is ongoing controversy about the clinical criteria that define a case.

For surveillance purposes only, the Centers for Disease Control and Prevention defines a case of Lyme disease as any patient with a physician-diagnosed erythema migrans rash at least 5 cm in diameter or specific musculoskeletal, cardiac, or neurologic manifestations and a serologic test positive for *B burgdorferi*.[9] During the five-year period 1983 to 1987, a passive surveillance system in California identified 399 autochthonous cases of Lyme disease meeting these criteria (unpublished data). These cases were reported primarily from the northwestern coastal counties of the state. To determine a more accurate incidence of Lyme disease in this endemic region, we implemented an active surveillance program in July 1991. We present here the characteristics of all patients suspected of having Lyme disease who were identified in the active surveillance area during the 18-month period from July 1, 1991, to December 31, 1992.

Patients and Methods

The region covered by the active surveillance program is located in northwestern coastal California. It occupies

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18,710 km² (7,224 sq mi) in total area and includes Lake, Mendocino, Sonoma, and the southern half of Humboldt counties. The area includes a variety of habitats but generally forms a patchwork of Mediterranean chaparral, redwood forest, and cultivated lands. *Ixodes pacificus* is focally abundant throughout the region (J. Clover, California Department of Health Services, oral communication, October 1992). Most of the 531,366 inhabitants live in rural areas and are involved primarily in agriculture, forestry, government, and the retail and service industries.[10]

All medical care professionals in the area thought likely to diagnose and treat cases of Lyme disease were invited to participate in the surveillance program. These included general practitioners, internists, dermatologists, rheumatologists, medical staff at primary and tertiary care centers, and other physicians specializing in the diagnosis and treatment of Lyme disease. They were identified through medical societies, previous reporting to the California Department of Health Services, and commercial listings. All enrolled professionals were telephoned monthly to list any patients who were suspected of having or who had been treated for presumptive Lyme disease during the previous month.

Data collected either over the telephone or by chart review at the medical office included, for each patient, the following: demographic information; presenting symptom(s); history of recent tick bite(s), with the geographic location where the bite occurred; all signs and symptoms, particularly dermatologic, musculoskeletal, neurologic, and cardiac manifestations; laboratory test results, if any; treatment regimen, if given; and the classification of the condition by the medical care professional as a probable, possible, or unlikely case of Lyme disease.

For surveillance purposes, all incident cases were assumed to have received exposure in the previous 30 days, as they resided in a known endemic area. An incident or early case of Lyme disease was defined as any patient with physician-diagnosed erythema migrans. This criterion was chosen to allow the comparison of incidence rates in California with those in other areas of the United States. As the size of the rash was not available for many suspected cases, estimates of incidence were calculated using three different numerators:

- Only those cases meeting national surveillance case criteria—that is, patients with physician-diagnosed erythema migrans of at least 5 cm in diameter (minimum number of cases)[9];
- All cases of physician-diagnosed erythema migrans regardless of rash size (maximum number of cases);
- All cases meeting national surveillance case criteria plus a proportion of those cases missing information on rash size. We defined this proportion of additional cases as equal to the number of patients with erythema migrans of at least 5 cm in diameter over the total number of persons with erythema migrans of a known size.

A case of prevalent or late-stage Lyme disease that met national surveillance criteria was defined as any patient with specific musculoskeletal, cardiac, or neurologic manifestations and with a serologic test positive for antibodies to *B burgdorferi*.[9]

Results

A total of 205 medical care professionals participated in the surveillance program, of whom 94% were enrolled in 1991. From July 1, 1991, through 1992, Lyme disease presumed to have been contracted in California was suspected in 319 persons through the active surveillance program. Of these patients, 49% resided in Mendocino County, 29% in Sonoma County, 15% in southern Humboldt County, 6% in Lake County, and 3% in adjacent counties (cases from adjacent counties were excluded from the calculation of rates). The ages of patients with suspected Lyme disease ranged from 1 to 86 years (median, 41), and 55% were female.

Incident Cases

Of the 57 patients diagnosed with erythema migrans by a physician, 42 had information on the rash size (Table 1). Of these 42 cases, 33 (78%) reported a rash size of 5 cm or greater in diameter and thus met national surveillance case criteria for incident Lyme disease. We assumed that this same proportion, 78%, of the 15 cases lacking information on erythema migrans size also met national surveillance case criteria. Excluding the one patient who lived in an adjacent county, the annual incidence of physician-diagnosed erythema migrans, estimated using different numerators as outlined earlier, ranged from 4.0 to 7.0 cases per 100,000 population (Table 2). Of the 57 cases of erythema migrans, 43 had a history of a recent tick bite; of these 43 patients, 14 were bitten at least three days before the onset of the rash (24 unspecified). Of the 57 patients, 43 were classified by a physician as probable or possible cases of Lyme disease; 54 were treated with antibiotics. Although cases occurred throughout the year, Lyme disease was diagnosed most often in the spring and summer months (Figure 1). Of all the cases of physician-diagnosed erythema migrans regardless of rash size, the age-specific annual incidence ranged from 1.9 to 11.9 cases per 100,000 population (Table 3). The county-specific annual incidence, again using all cases of physician-diagnosed erythema migrans, ranged from 2.1 to 65.7 cases per 100,000 population (Table 4).

A total of 43 patients were diagnosed with a suspicious rash not defined by the physician as erythema migrans (Table 1). Of these 43 patients, 33 recalled a recent tick bite (4 unspecified); 8 had a rash greater than 5 cm in diameter (21 unspecified); and the rash had occurred more than three days after the known bite for 8 patients (15 unspecified). Of these 43 patients, 27 were classified by the physician as probable or possible cases of Lyme disease, and 40 patients were treated with antibiotics. These cases were not included in any of the estimates of incidence.

In all, 41 patients presented with flulike symptoms that included fever, headache, and arthralgias, myalgias, or both (Table 1). Of these patients, 28 recalled a tick bite,

TABLE 1.—*Characteristics of Suspected Cases of Incident Lyme Disease in Northwestern Coastal California, July 1991 to December 1992*

	Patients, No. (%)					
	Erythema Migrans		Suspicious Rosh Not Diagnased as Erythema Migrans		Flulike Symptoms Without Rash ar Tick Bite	
Characteristic	n=57*	95% CI	n=43	95% CI	n=53	95% CI
Size of skin lesion						
≥5 cm	33 (58)	44-70	8 (19)	9-34	NA	
<5 cm	9 (16)	8-29	14 (33)	20-49		
Unspecified	15 (26)	16-40	21 (49)	34-64		
Meets national surveillance case criteria†						
Yes	33 (58)	44-70	NA		NA	
No	9 (16)	8-29				
Insufficient information	15 (26)	16-40				
Known tick bite						
Yes	43 (75)	62-85	33 (77)	61-88	40 (75)	61-85
No	12 (21)	5-24	6 (14)	6-29	9 (17)	9-30
Unspecified	2 (4)	1-14	4 (9)	3-23	4 (8)	3-20
Time from known bite to rash onset						
≥3 days	14 (33)	22-47	8 (15)	7-30	12 (30)	19-44
<3 days	5 (12)	5-24	10 (30)	18-46	14 (35)	23-49
Unspecified	4 (45)	16-40	15 (45)	30-61	14 (35)	23-49
Treated with antibiotics						
Yes	54 (95)	85-99	40 (93)	80-98	51 (96)	86-99
No	0 (0)		2 (5)	1-18	1 (2)	0-12
Unspecified	3 (5)	1-15	1 (2)	0-13	1 (2)	0-12
Borrelia burgdorferi serologic results						
Positive	11 (19)	10-32	10 (23)	12-39	18 (34)	22-43
Borderline	4 (7)	2-18	2 (5)	1-18	4 (8)	3-20
Negative	10 (18)	10-31	11 (26)	14-42	12 (23)	13-37
Not tested or unknown	32 (56)	42-69	20 (47)	32-63	19 (36)	24-50
Classification by physician						
Probable case	27 (47)	34-61	4 (9)	3-23	14 (26)	15-40
Possible case	16 (28)	17-42	23 (53)	37-68	17 (32)	20-46
Unlikely case	2 (4)	1-14	11 (26)	14-42	15 (28)	17-42
Unspecified	12 (21)	12-34	5 (12)	5-26	7 (13)	6-26

CI = confidence interval, NA = not applicable

*One patient resided in an adjacent county.
†Rash size ≥5 cm; exposure occurred in an endemic county.

and the symptoms began at least three days after the bite in 12 patients (13 unspecified). Of these 41 patients with flulike symptoms, 29 were classified by their physicians as probable or possible cases of Lyme disease; 40 patients were treated with antibiotics. Again, these cases were not included in any of the estimates of incidence.

The incidence using alternative criteria to national surveillance criteria may be calculated from these data. For example, 27 patients with erythema migrans, 4 with suspicious rashes, and 14 with flulike symptoms were classified as probable cases of Lyme disease by their physician (Table 1). Using these 45 cases of suspected incident Lyme disease, we estimated the annual incidence of probable Lyme disease as 5.6 cases per 100,000 population.

Twelve patients who were asymptomatic presented with a history of a tick bite during the previous two days. One of these patients was treated with antibiotics because the tick had been identified as positive for *B burgdorferi;* the attachment time of this tick was not known. The other 11 patients were treated with a course of antibiotics at their own request.

Prevalent Cases

The remaining 166 patients presented with symptoms considered by their physicians as consistent with a diagnosis of prevalent or late Lyme disease (Table 5). Of these, 51 patients presented with specific symptoms, including 37 patients with arthritis. Of these 51 suspected cases, 37 were classified as probable and possible cases of Lyme disease (Table 6); all 51 patients were treated with antibiotics. Only 34 of these 51 patients met national surveillance case criteria for Lyme disease.

Finally, 115 patients presented with only one or more nonspecific symptoms, including arthralgias, myalgias, fatigue, paresthesias, and confusion, depression, or both. These patients were classified into two groups: those who

TABLE 2.—*Annual Incidence of Physician-Diagnosed Erythema Migrans (EM) in Northwestern Coastal California, July 1991 to December 1992*

Numerator of EM Cases	*Patients (n=57), No.*	*Annual Incidence/ 100,000* (95% CI)*
Physician-diagnosed EM in persons residing in the study area	56†	7.0 (6.77-7.22)
Information on size available	41	
Meets national surveillance case criteria‡	32	4.0 (3.83-4.17)
Proportion of cases with information on size meeting national surveillance case criteria	0.78	
Missing information on size	15	
Proportion with missing information on size assumed to meet national surveillance case criteria	0.78	
Missing information assumed to meet national surveillance case criteria	12	
Both meets and assumed to meet national surveillance case criteria	44	5.5 (5.30-5.70)

CI = confidence interval

*From the Bureau of the Census.[10]
†Excludes the 1 patient living in an adjacent county.
‡Rash size ≥5 cm; exposure occurred in an endemic county.

presented with arthralgias as the predominant complaint, and those who presented with other nonspecific symptoms. Of the 83 patients with arthralgias, 64 were seropositive for *B burgdorferi* (Table 5). These patients were classified as having probable (38), possible (35), or unlikely (7) cases of Lyme disease (3 unspecified), and all were treated with antibiotics. Of the 32 patients presenting with nonspecific symptoms other than arthralgias, including fatigue, depression, confusion, or paresthesias, 26 were seropositive. In all, 13 patients were considered probable cases, and 14 were considered possible cases of Lyme disease; 20 were treated with a course of antibiotics.

Discussion

Using active surveillance in an area of California considered endemic for Lyme disease, we ascertained the occurrence of 153 suspected incident and 166 suspected prevalent cases during the 18-month period July 1991 through December 1992. Of these 319 suspected cases, 94% were treated with antibiotics. Only 21% met national surveillance case criteria for Lyme disease, however.

For surveillance purposes, the most sensitive and specific criterion for incident Lyme disease is physician-diagnosed erythema migrans.[11] In this study, 57 patients were diagnosed with erythema migrans by a medical care professional; of these cases, however, only 33 of 42 with information on rash size met national surveillance case criteria. When we assumed that the same proportion, 78%, of the remaining 15 cases lacking information on erythema size also met national surveillance case criteria, the cumulative annual incidence of physician-diagnosed erythema migrans was estimated to be 5.5 cases per 100,000 population in this area of northwestern coastal California.

TABLE 3.—*Age-Specific Incidence Rates of Erythema Migrans in Northwestern Coastal California, July 1991 to December 1992*

Age, years	*Patients, No.*	*Population Size**	*Annual Incidence/ 100,000 (95% CI)*
0-9	11	78,607	9.3 (8.6-10.0)
10-19	7	68,053	6.9 (6.3-7.6)
20-29	2	70,146	1.9 (1.6-2.3)
30-39	7	94,593	4.9 (4.5-5.4)
40-49	14	78,501	11.9 (11.2-12.7)
50-59	5	43,690	7.6 (6.8-8.5)
60-69	4	45,566	5.9 (5.2-6.7)
70+	6	52,120	7.7 (7.0-8.5)
Total	56	531,276	

CI = confidence interval

*From Bureau of the Census.[10]

TABLE 4.—*County-Specific Annual Incidence of Erythema Migrans in Northwestern Coastal California, July 1991 to December 1992*

County	*Patients, No.*	*Population Size*	*Annual Incidence/ 100,000 (95% CI)*
Humboldt, southern half	12	12,168	65.7 (61.4-70.3)
Lake	3	50,631	4.0 (3.5-4.6)
Mendocino	29	80,345	24.1 (23.1-25.5)
Sonoma	12	388,222	2.1 (2.0-2.3)
Total	56	531,366	

CI = confidence interval

For the 26 cases of physician-diagnosed erythema migrans with data available, the median time from a known bite to the appearance of erythema was seven days. This compares with a median of seven to nine days for cases of erythema migrans diagnosed in the endemic Atlantic northeastern United States.[11,12] It is possible that some rashes classified by physicians as erythema migrans were, in fact, allergic reactions to tick bites that occur immediately after the bite. Including allergic reactions as cases of erythema migrans would inflate its estimated incidence in this area.

Few studies have examined risk factors for Lyme disease in California.[13,14] *Ixodes pacificus* is focally endemic throughout the northwestern coastal counties and is active throughout most of the year. Most cases of erythema migrans reported actively from the surveillance area in 1992 occurred in the spring and summer months, when nymphal ticks are most common, suggesting that this immature stage, small and easily overlooked, is important in transmitting Lyme disease. Children aged 1 to 9 years were at high risk of erythema migrans, suggesting that exposure to ticks may occur primarily around the home. Al-

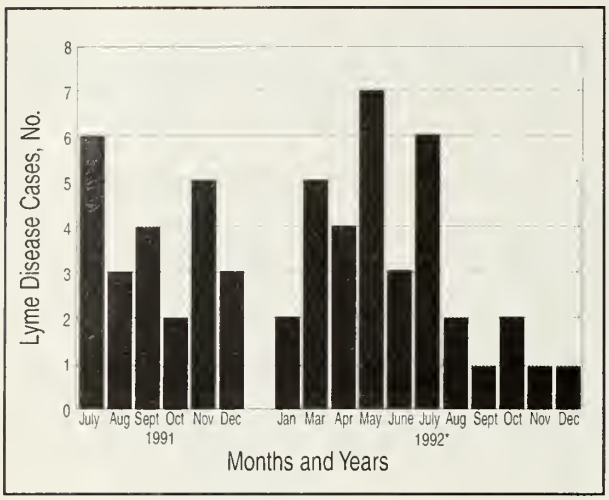

Figure 1.—The graph shows the temporal distribution of cases of physician-diagnosed erythema migrans as ascertained by active surveillance in northwestern coastal California, July 1991 through December 1992. *No cases of erythema migrans were diagnosed in February 1992.

ternatively, however, given the high infection rate in persons aged 40 to 49, exposure may also occur in the work environment.

In this study, 63% of patients with suspected incident cases had only nonspecific symptoms, including flulike symptoms or a suspicious rash not classified by a physician as erythema migrans. Most of these patients (60%) were classified as having probable or possible Lyme disease and treated with antibiotics as a precautionary measure. Because such patients are excluded by the surveillance criteria, the actual incidence of Lyme disease in this area may be seriously underestimated.

Antibiotics were prescribed to 12 patients with a history of a tick bite but no signs or symptoms of Lyme disease. The prophylactic treatment of tick bites is not routinely indicated, as treatment after symptoms of Lyme disease develop is sufficient to resolve an initial infection.[15] Furthermore, in California the risk of Lyme disease following a single tick bite is probably less than 1%, because the prevalence of *B burgdorferi* infection in the tick vector is on the order of 1% to 2%,[4] and an infective tick most probably must be attached to its animal host for 24 to 48 hours before *B burgdorferi* is to be transmitted.[16,17] It is important that persons in the surveillance area understand the extremely low probability of contracting Lyme disease in California after a single tick bite.[18]

Only 34 (20%) of 166 patients suspected of having prevalent or late-stage Lyme disease in this study met national surveillance case criteria; 25 of these 34 cases (74%) were diagnosed with arthritis. Most of the remaining 115 patients who did not have any of the specific musculoskeletal, neurologic, or cardiac manifestations of late Lyme disease presented with nonspecific symptoms, and it appears that many were diagnosed with Lyme disease based primarily on their positive serologic test results. Most of these patients were treated with antibiotics, and several received long-term therapy. Based on these findings, we think that some patients in this region may be treated unnecessarily for suspected Lyme disease. Other diseases, such as fibromyalgia and chronic fatigue syndrome, produce nonspecific symptoms similar to those of Lyme disease and should be considered as possible diagnoses.[3]

TABLE 5.—*Characteristics of Suspected Cases of Lyme Disease, July 1991 to December 1992*

Characteristics	Patients, No.	Serologic Borrelia burgdorferi Test Results: Positive	Borderline	Negative
Specific symptoms				
Arthritis	37	25		11
Facial palsy	8	4	3	1
Atrioventricular block	1	1		
Meningoencephalitis	2	2		
Facial palsy and arthritis	1	1		
Encephalitis	1	1		
Atrioventricular block	1	1	1	
Nonspecific symptoms				
Arthralgia	83	64	10	
Myalgia	15			
Other complaints	32	26		4
Total	166	124	14	16
Meet CDC surveillance case criteria	34	34		

CDC = Centers for Disease Control and Prevention

TABLE 6.—*Classification by the Physician of Patients With Suspected Lyme Disease by Presence of Specific or Nonspecific Symptoms*

Classification	Patients, No.: Specific Symptoms*	Nonspecific Symptoms
Probable Lyme disease	25	51
Possible Lyme disease	12	49
Unlikely Lyme disease	2	11
Unspecified	12	4
Total	51	115

*Specific symptoms include arthritis, facial palsy, atrioventricular block, and meningitis.

Several limitations are inherent in any study involving active surveillance. First, results are not comparable to those of passive surveillance. At least one other active surveillance program for Lyme disease has been implemented, in a hyperendemic area of Connecticut; the incidence of Lyme disease there was shown to be 560 cases per 100,000 population in 1992 (M. Cartter, MD, Connecticut Health Division, oral communication, October 1993). This comparison of rates using the same criteria suggests that Lyme disease in California, although endemic, is most probably present at a substantially lower rate than in the Atlantic northeastern United States. Second, the active surveillance program did not encompass all medical care professionals practicing in the northwestern coastal counties. Any case of Lyme disease diagnosed by a physician not included in the program or reported by passive surveillance would be missed, leading to an un-

derestimate of the incidence in this area. If we include the 21 cases ascertained by passive surveillance from the surveillance area, the annual incidence of physician-diagnosed erythema migrans was 8.2 cases per 100,000 population. Third, only cases that come to medical attention will be included in an estimate of incidence. It is not possible to determine the proportion of patients with Lyme disease in this area of California who did not seek medical care. Fourth, because physicians and patients were not called when information was missing from the medical record, data may be incomplete, leading to unreliable estimates of incidence. Most important, a diagnosis of Lyme disease is difficult to substantiate by medical record review. Given these limitations, the true incidence of Lyme disease in these northwestern coastal counties of California may be higher than the estimate calculated in this study.

Surveillance criteria for Lyme disease are designed for high specificity and thus have lower sensitivity. Although persons who do not have the disease are more likely to be correctly excluded from the calculated rates, actual cases of disease are also more likely to be excluded. These criteria are not intended to be used as a guide for clinical diagnosis and treatment. Instead, they provide a systematic method of assessing the effects of Lyme disease in an area and allow a comparison of rates between years and between geographic areas. Although the use of alternative criteria to those used by the Centers for Disease Control and Prevention for surveillance purposes may produce a different estimate of incidence, it does not allow the comparison of the rate of Lyme disease in California with that of other areas of the United States.

In conclusion, surveillance criteria for Lyme disease appear to exclude a large proportion of cases of Lyme disease diagnosed in California from July 1991 through 1992. An argument could be made to expand the surveillance criteria so that more patients with nonspecific symptoms are included, but we do not think they should be changed, as it is possible that most of these cases are misdiagnosed.[19,20] Until a standardized, highly sensitive and specific laboratory test is available for national surveillance purposes, many patients in California presenting with nonspecific signs and symptoms who are currently diagnosed with suspected Lyme disease will be excluded from any measures of incidence or prevalence.

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Articles

Prevalence of HTLV Types I and II Among Drug Users in King County, Washington

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We investigated the prevalence of human T-cell lymphotropic virus (HTLV) types I and II among drug users entering treatment in King County, Washington, between 1988 and 1990. Of 762 injection-drug users, 81 (10.6%) were HTLV-positive; of 89 noninjection-drug users, 2 (2%) were HTLV-positive. Most (95.8% of those typed) were HTLV-II-positive. The relationship between HTLV and demographic and behavioral characteristics was further evaluated among injection-drug users. The prevalence rates for HTLV increased 25-fold from the youngest age group (15 to 24 years) to the oldest (older than 45 years), after adjusting for race. After adjustment for age, American Indians or Alaska Natives were 7.9 times, blacks 6.2 times, Asians or Pacific Islanders 4.7 times, and Hispanics 4.1 times as likely as whites to be HTLV-positive. The prevalence of HTLV among heroin injectors was more than double that observed among injectors of other drugs after adjusting for age, although this association was only marginally significant. The strong association between HTLV prevalence and age suggests that HTLV-II (the predominant virus) has been endemic among King County injection-drug users for some time. Its relatively high prevalence indicates that there is both an opportunity and a need to further investigate the epidemiologic and clinical implications of HTLV-II infection.

(Thiede H, Harris NV, McGough JP, Roberts B, Khabbaz RF, Kaplan JE: Prevalence of HTLV types I and II among drug users in King County, Washington. West J Med 1994; 160:540-544)

Human T-cell lymphotropic virus (HTLV) type I, first reported in 1980,[1] has been linked to adult T-cell leukemia and to tropical spastic paraparesis.[2,3] Many HTLV-I infections occur in the absence of any clinical symptoms, leaving open to question the full clinical effects of this infection.[2] In the 1980s another closely related retrovirus, HTLV type II, was isolated from two patients with a variant of hairy cell leukemia.[4,5] This retrovirus has not been clearly associated with any specific clinical manifestations, however.

Infection with HTLV-I has been reported from many parts of the world and is endemic in southwestern Japan, the Caribbean, and parts of Africa.[2] In the United States, HTLV-I infection has been identified primarily in persons born in, or reporting sexual contact with, persons from HTLV-I endemic areas,[6,7] but also in injection-drug users[8,9] and patients of sexually transmitted disease (STD) clinics.[8] The retrovirus HTLV-II has been identified mainly in injection-drug users,[7-9] their sex partners,[7] STD clinic patients,[8] and various American Indian groups.[10-15] Type I is transmitted sexually (more easily from man to woman),[16,17] from mother to child (primarily by breast-feeding),[2,16] and parenterally through blood transfusion[2,18] or injection-drug use.[3] Type II is presumed to be transmitted similarly.

A prevalence study of HTLV types I and II (HTLV) conducted in eight metropolitan areas in 1988 and 1989 showed that injection-drug users entering drug treatment in the Seattle and King County areas of Washington State had the third highest HTLV prevalence (9.4%), after Los Angeles (17.6%) and New Orleans (14.4%).[8] Seattle, the largest city in Washington, is located in King County, which has a population of about 1.5 million. As many as 22,000 King County residents are estimated to have injected illicit drugs at least once since 1978 (Seattle-King County Department of Public Health, unpublished data). To explore the risk factors for infection with HTLV among injection-drug users in Seattle and King County as well as the difference in HTLV seroprevalence between drug users who inject drugs and those who do not,* we analyzed data on drug users entering treatment during six quarters between September 1988 and July 1990.

*See also the editorial by B. Hjelle, MD, "HTLV-II Infection in the Western United States," on pages 576-577 of this issue.

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
CI = confidence interval
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus
HTLV = human T-cell lymphotropic virus
OR = odds ratio
STD = sexually transmitted disease

Patients and Methods

The methods for this study have been described in detail elsewhere[8,19,20] and are briefly summarized here.

Data Collection and Study Population

Leftover blood specimens collected for routine clinical purposes from clients entering drug treatment at six facilities in King County in six quarters between September 1988 and December 1990 were used as part of the national Centers for Disease Control and Prevention (CDC) human immunodeficiency virus (HIV) seroprevalence surveys. Serum specimens were linked by an anonymous code to demographic, sexual, and drug-injection information abstracted from client charts by study personnel.[8,19,20] Specimens from patients admitted to the same treatment site for the second time in a year or for alcohol use only and those from persons with an unknown route of drug administration were excluded. Injection-drug use was defined as the use of one or more injection drugs in the past 12 months and noninjection-drug use as the absence of injecting drugs since 1978 and the use of one or more noninjectable drugs in the past 12 months.

To estimate the prevalence of HTLV among drug users, two subsets of blood specimens collected from drug users enrolled in the HIV seroprevalence survey between 1988 and 1991 were tested for HTLV antibodies. The first subset (n = 493) consisted of all subjects with available blood specimens who were enrolled in the HIV survey in the past two quarters of 1988 and the first two quarters of 1989. Data from this subset were also included in the aforementioned HTLV prevalence study conducted in eight metropolitan areas.[8] The second subset consisted of 269 subjects who were consecutively entered in the HIV survey within the first two quarters of 1990. Before 1990, only injection-drug users were included in the survey. In 1990, however, the HIV serosurvey protocol was changed, and 89 noninjection-drug users who entered treatment consecutively during the latter period were also surveyed.

Laboratory Testing

The serum specimens were tested for antibodies to HTLV at the Retrovirus Diseases Branch of the CDC. They were first screened with an HTLV-I enzyme-linked immunosorbent assay (ELISA, DuPont Merck Pharmaceutical Company). Repeatedly reactive serum was further tested by Western blot and radioimmunoprecipitation assay.[8,21] Specimens demonstrating reactivity to *gag* p24 and *env* gp 46 or gp 61/68 by Western blot or radioimmunoprecipitation assay were considered positive. Those showing one or more viral bands but not satisfying these criteria were designated indeterminate. All other specimens were considered negative. For HTLV-positive specimens, type I was differentiated from type II by synthetic peptide-based ELISA tests (SynthEIA HTLV-I EIA RV900250 and HTLV-II EIA RV900750, United Biomedical).[8,22] Another peptide-based ELISA (Select-HTLV B-005, IAF Biochem International, Montreal) was used to differentiate specimens that could not be successfully typed by the first tests. Testing for the HIV antibody was done by the Seattle-King County Department of Public Health Laboratory by enzyme immunoassay (Genetic Systems). For serum specimens that were repeatedly reactive for HIV antibodies by enzyme immunoassay, the results were confirmed by Western blot (DuPont).

Analysis

We determined the seroprevalence of HTLV among the 762 injection-drug users and the 89 noninjection-drug users. Two injection-drug users with indeterminate HTLV results were included in the denominator for calculating the overall HTLV prevalence rate, but excluded from all other analyses. Among injection-drug users, we calculated HTLV prevalence by demographic characteristics, sexual orientation (as determined by reported gender of sex partners since 1978), and drugs injected. Unconditional logistic regression analyses[23] were used to estimate the odds ratio (OR) while adjusting for possible confounding factors. Variables that were associated with HTLV infection were considered possible confounders. The adjusted odds ratios are presented whenever the inclusion of possible confounding factors altered the odds ratio by 25% or more. Variations of effects across strata were evaluated by stratified analyses.[24]

Results

The prevalence of HTLV was higher among injection-drug users than among noninjection-drug users. Of 762 injection-drug users entering treatment, 81 were HTLV-positive (10.6%; 95% confidence interval [CI]) = 8.4% to 12.8%) compared with 2 of 89 noninjection-drug users (2.2%; 95% CI = 0.3% to 7.9%) entering the same drug treatment centers in 1990.

Of the 81 HTLV-positive injection-drug users, infection could be typed in 70 (86%). Of these, 3 (4%) were HTLV-I positive (all were of Asian or Pacific Islander race or ethnicity), and 67 (96%) were HTLV-II positive. Six HTLV-positive specimens were not tested, and five could not be differentiated. One of the HTLV infections in noninjection-drug users was due to HTLV-II, and the other could not be typed.

Of the 762 injection-drug users, 19 (2.5%; 95% CI = 1.4% to 3.6%) were HIV-positive, but only 1 of those was also coinfected with HTLV (OR = 0.5; 95% CI = 0.0 to 3.3) (Table 1).

Among injection-drug users, the HTLV prevalence was four to eight times higher among nonwhites than among whites (Table 1). Compared with whites and after

TABLE 1.—*Prevalence of Human T-Cell Lymphotropic Virus (HTLV) Among Injection-Drug Users Entering Treatment in King County, Washington, 1988 to 1990*

Demographic Characteristics and Risk Behaviors	*No. HTLV Positive/No. Tested (%)**	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Sex			
Male	55/468 (11.8)	1.0	1.0
Female	24/286 (8.4)	0.7 (0.4-1.2)	0.9 (0.5-1.5)†
Sexual orientation			
Heterosexual female	21/248 (8.5)	1.0	1.0
Heterosexual male	52/399 (13.0)	1.6 (0.9-2.9)	1.2 (0.7-2.2)‡
Gay or bisexual male	1/25 (4.0)	0.5 (0.0-3.4)	0.6 (0.1-4.9)‡
Lesbian or bisexual female	0/9 (0.0)	0.0 (0.0-5.9)§	0.0 (0.0-9.8)‡§
Race or ethnicity			
White	26/548 (4.7)	1.0	1.0
Black	43/156 (27.6)	7.6 (4.4-13.4)	6.2 (3.6-10.8)†
Hispanic	5/26 (19.2)	4.8 (1.5-14.9)	4.1 (1.4-12.5)†
Asian or Pacific Islander	3/13 (23.1)	6.0 (1.3-25.9)	4.7 (1.2-19.2)†
American Indian or Alaska Native	3/13 (23.1)	6.0 (1.3-25.9)	7.9 (2.0-32.2)†
Age, years‖			
15-24	1/78 (1.3)	1.0	1.0
25-29	9/144 (6.2)	5.1 (0.6-110.3)	5.3 (0.6-43.5)‡
30-34	12/202 (5.9)	4.9 (0.6-101.9)	3.5 (0.4-27.8)‡
35-39	20/184 (10.9)	9.4 (1.2-191.3)	6.8 (0.9-52.7)‡
40-45	21/97 (21.6)	21.3 (2.5-435.4)	14.9 (1.9-116.4)‡
>45	16/43 (37.2)	45.6 (4.6-966.9)	25.2 (3.1-205.8)‡
Homeless¶			
No	54/451 (12.0)	1.0	
Yes	8/102 (7.8)	0.6 (0.3-1.4)	
HIV infection			
No	80/741 (10.8)	1.0	
Yes	1/19 (5.3)	0.5 (0.0-3.3)	

CI = confidence interval, HIV = human immunodeficiency virus, OR = odds ratio

*Total number of subjects may vary because of missing information for some subjects.
†Adjusted for age (15 to 24 years versus 25 to 39, 40 and older).
‡Adjusted for race (white versus nonwhite).
§Exact confidence intervals.
‖$P_{trend} < .01$.
¶Homeless is defined as someone without a permanent address.

adjusting for age, American Indians or Alaska Natives had the highest odds ratio (7.9), followed by blacks (6.2), Asians or Pacific Islanders (4.7), and Hispanics (4.1).

There was a strong trend of increasing HTLV prevalence with increasing age (Table 1). Compared with those 15 to 24 years old and after adjusting for race, those 25 to 29 years old were more than 5 times, those 30 to 34 years old more than 3 times, those 35 to 39 years old nearly 7 times, those 40 to 45 years old almost 15 times, and those older than 45 years more than 25 times more likely to be HTLV-positive.

After adjustment for age, heroin injectors were more than twice as likely to be HTLV-positive compared with injectors of other drugs, although this difference was only marginally significant (OR = 2.3; 95% CI = 0.9 to 5.9) (Table 2). Adjusting for race did not alter the odds ratio.

No difference in HTLV seropositivity was observed by year of survey, survey site, sex, sexual orientation, homelessness, or use of drugs other than heroin (regardless of route of administration).

Discussion

The prevalence of HTLV was higher among injection-drug users than among noninjection-drug users, although transmission by drug injection before 1978 cannot be ruled out. As in other studies of injection-drug users that differentiated between HTLV-I and HTLV-II,[8,9] type II infection accounted for most of the HTLV infections in the group surveyed. Restricting the analysis to confirmed HTLV-II-positive and HTLV-negative subjects did not change any of our results appreciably.

Our findings with regard to risk factors for HTLV are consistent with those from studies done in other parts of the country in that HTLV prevalence increased with age,[8,25-27] HTLV was more prevalent among nonwhites than among whites,[8,26-28] and the prevalence was higher among heroin injectors than among injectors of other drugs.[8] The observed pattern of increased HTLV prevalence in older age groups is most likely due to a longer duration of injecting drugs,[29] although a cohort effect such as differences in needle-sharing patterns between different age groups cannot be ruled out.

We did not find HTLV to be associated with HIV. Similarly, the risk factors for HTLV and HIV infection differed, with the exception of the increased risk for both infections observed for nonwhite injection-drug users.

TABLE 2.—*Prevalence of Human T-Cell Lymphotropic Virus (HTLV) by Injection-Drug Characteristics*

Injection Drug	*No. HTLV-Positive/No. Tested (%)**	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Heroin			
No	5/125 (4.0)	1.0	1.0
Yes	76/635 (12.0)	3.3 (1.2-9.4)	2.3 (0.9-5.9)†
Cocaine			
No	30/348 (8.6)	1.0	1.0
Yes	51/412 (12.4)	1.5 (0.9-2.5)	1.0 (0.6-1.7)‡
Amphetamine			
No	77/688 (11.2)	1.0	1.0
Yes	4/72 (5.6)	0.5 (0.1-1.4)	1.5 (0.5-4.9)†‡§
"Speedball"‖			
No	77/723 (10.7)	1.0	
Yes	4/37 (10.8)	1.0 (0.3-3.1)	

CI = confidence intervals, OR = odds ratio

*Total number of subjects may vary because of missing information for some subjects.
†Adjusted for age (15 to 24 years versus 25 to 39 years, 40 and older).
‡Adjusted for race (white versus nonwhite).
§Adjusted for heroin injection (yes versus no).
‖Street name for cocaine plus heroin.

Among the larger sample of injection-drug users entering these treatment facilities between 1988 and 1991, HIV infection was also associated with sex between men, amphetamine injection, reported homelessness, and younger age (25 to 34 versus 35 and older).[20] Increased HTLV prevalence among HIV-positive injection-drug users has been reported in the United States, mostly from East Coast cities,[8,25] whereas studies reported from some western cities have not observed such an association.[8,28] The lack of an association between HIV and HTLV among Seattle and King County injection-drug users may reflect differences in HIV epidemiology in the West where sex between men still accounts for most cases of infections. By contrast, in eastern cities, HIV is frequently transmitted through injection-drug use. It could also be due to a lack of statistical power in studies conducted in the West, where HIV prevalence among injection-drug users is relatively low.

The following possible limitations should be considered when interpreting the findings of this study:

- Its cross-sectional design,
- The potential for more than one observation on individual drug users,
- The representativeness of the study population,
- Possible limited detection of HTLV-II, and
- The restriction to data from client charts.

The cross-sectional design makes it difficult to assess the temporal relationships between reported drug-injecting behaviors and the acquisition of HTLV infection. To assess the validity of using recent drug use as a surrogate for drugs used before HTLV infection, we reviewed the records of 105 systematically selected injection-drug users entering treatment at the participating facilities in May 1992. The findings of this review indicated that drug-use patterns were relatively long-standing. None of the 105 had changed their primary drug of choice since 1986, the earliest time for which this type of information was available. Among the larger sample of injection-drug users surveyed for the HIV seroprevalence studies between 1988 and 1991, more than half reported having injected drugs longer than ten years, and only 22.3% reported having injected for less than six years.[20] Thus, some aspects of recent drug-use behavior may be reasonable surrogate measures of earlier patterns.

Individual drug users could have been surveyed more than once if they entered different treatment facilities in the same year or if they entered treatment in more than one year. The review of 105 injection-drug users mentioned earlier revealed that 9% could have been entered in the larger HIV prevalence study more than once between 1988 and 1991. This estimate is based on a retrospective review of a four-year period, whereas data used for the present study were collected in six quarters between September 1988 and July 1990, further reducing the possibility of multiple observations on persons. It is uncertain how any such repeated observations would affect the results if they occurred.

We estimate that the participating drug treatment centers serve between 60% and 70% of injection-drug users entering treatment in King County and that 90% of eligible injection-drug users entering participating sites were included in the HIV seroprevalence surveys.[20] Thus, the subset of subjects sampled for the HTLV survey was drawn from a larger pool, which represented more than half of injection-drug users entering treatment in King County, Washington, during the survey period. When the subset of injection-drug users in the HTLV study was compared with the larger study group of injection-drug users in the HIV seroprevalence survey between 1988 and 1991, the HTLV study group was younger, less likely to inject heroin, and had a higher proportion of gay or bisexual men (data not shown). Because HTLV infection was associated with older age and heroin injection, the HTLV prevalence reported for the current survey population may underestimate the prevalence in injection-drug users entering treatment in King County. A limited sensitivity of HTLV-I antibody assays to HTLV-II has been reported[30] and may also have contributed to an underestimation of HTLV (specifically HTLV-II) prevalence in this and other studies.

Groups not represented in the current survey (injection-drug users seeking treatment at smaller, private drug-treatment settings, or those not seeking treatment) may differ from groups surveyed with regard to HTLV prevalence. In another local study of injection-drug users, 14.8% of white and 35.0% of nonwhite drug users sampled from the "street" were HTLV-positive (Jane Schwebke, MD, University of Washington Center for AIDS [acquired immunodeficiency syndrome] and STD, unpublished data, 1992), compared with 4.7% and 26.0%, respectively, in our study of injection-drug users entering treatment. Had the sample in the current study included injection-drug users not in treatment, the prevalence may have been higher than that reported, whereas including drug users en-

tering smaller private facilities may have yielded a lower HTLV prevalence.

Data were limited to information available in client records and did not include sexual practices such as condom use and number of sex partners or drug-use practices such as duration and frequency of use and needle-sharing habits. Longitudinal studies that gather more detailed information on clients' sexual and drug injection behaviors in relation to HTLV seroincidence are needed to further elucidate the epidemiologic characteristics of HTLV among injection-drug users.

Implications

Our findings suggest that HTLV-II is endemic among injection-drug users in the Seattle and King County area. Although HTLV viruses were not isolated until the early 1980s, they are known to have been present in this country since at least 1968.[31] The strong association between HTLV infection (mostly HTLV-II) and age suggests that HTLV has been present in injection-drug users longer than has HIV.

Both HTLV types I and II are bloodborne pathogens, evidently transmitted in ways similar to HIV, a relative newcomer. Even though the prevalence of HIV among Seattle and King County injection-drug users appears to have remained relatively low to date (at about 2.7%),[20] the higher prevalence of HTLV-II infection suggests that HIV could spread to a much greater extent in Seattle and King County and other West Coast locations where HTLV and HIV prevalence rates are similar to those described here. The prevalence of HTLV-II among Seattle and King County injection-drug users indicates both the need and the potential for further investigation of the epidemiology and the clinical manifestations of this infection.

Acknowledgment

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Conferences and Reviews

1492—The Medical Consequences

Discussant
CARLOS A. CAMARGO, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER BOUSHEY, MD*: *Although he has made important contributions in the field of endocrinology, Carlos Camargo, MD, is perhaps best known for the courses in the History of Medicine and the lectures in the Values, Technology, Science, and Society program that he teaches at Stanford University. In this conference, Dr Camargo discusses the far-reaching medical consequences of the epochal year of 1492.*†

CARLOS A. CAMARGO, MD‡: More than 500 years ago in October 1492, ninety Spaniards led by an Italian commander in three rather rickety vessels arrived at what would eventually be called America or the New World. The 500th anniversary of this event was commemorated by volumes of print describing and commenting on many aspects of the Columbian encounter. In this review I will focus primarily on its thought-provoking and important medical consequences and the demographic, cultural, and political phenomena that followed in the wake of the medical and nutritional exchanges of the 1492 encounter.

Within 50 years from the initial landing of a handful of Europeans on American soil ("America" will refer herein to its original geographical meaning—the name of the continent stretching from Alaska to Tierra del Fuego), huge areas of the continent had been conquered and mighty, sophisticated, and populous empires had been subdued. How a relatively small force of Spaniards could have conquered such huge empires in such a brief period has always been a mystery. In recent decades, important historical work begun by pioneers such as P. M. Ashburn, W. H. McNeill, A. W. Crosby, and others has helped to clarify both the causes and the consequences of this phenomenon.

Two Societies

Who were the two human groups that collided at the end of the 15th century? On the one side were the Spaniards coming from the most western peninsula of the Eurasian land mass, a peninsula where human and hominid habitation has been dated to at least half a million years ago. They were a people whose diverse ethnic origins included the ancient Iberians, Phoenicians, Carthaginians, Romans, Germanic tribes such as the Vandals and the Visigoths, and last but not least, as a result of the 711 AD invasion of Spain by Tariq, North African Moslems. For almost 800 years, a religious crusade to expel the Arab invaders had been taking place, culminating with the conquest of Granada on January 2, 1492. A few months later the Catholic monarchs, Ferdinand and Isabella, signed the final agreement with Christopher Columbus, opening the way for his first voyage.

On the other side, the Europeans encountered a group of humans who had rather recently arrived in the Western Hemisphere. Fully developed *Homo sapiens* had crossed the Beringian dry corridor between Asia and America several times during the past 30,000 years, taking advantage of the lowered sea level caused by glaciation in the late Pleistocene epoch. As the last ice age ended 10,000 years ago, the sea level rose to create the Bering Strait, and the new inhabitants of America became isolated from their counterparts in Asia. They had come to the American continent in small groups following big game and, in their passage through northeastern Siberia, had left behind many vectors of disease and disease pathogens. The harsh and cold climate of northeastern Asia has been referred to as the "Siberian filter" in this regard. Amerindians possessed no domesticated animals except for the llama in the South American Andes.

In cultural terms, the new inhabitants of the continent were not as homogenous as was their genetic makeup. Groups still in the Stone Age coexisted with advanced civilizations such as the Aztec, Inca, and Mayan. The last was without parallel in America. The Mayans' achievements in architecture, mathematics, and astronomy were impressive. In some areas they had surpassed the European cultures, being the first to develop the concepts of zero and of positional numeration. The Incas excelled in social organization, agricultural technology, and road building.

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†See also the editorial by G. B. Risse, MD, "What Columbus's Voyages Wrought," on pages 577-579 of this issue.

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Medicine and Religion in the Two Societies

At the end of the 15th century, European medicine was beginning to awaken from the slumber of the Middle Ages. Anatomical dissections had begun about 100 years before in Italian universities, and by the time of Columbus's voyage, a renaissance of anatomical knowledge was taking place in many parts of southern Europe. Unfortunately, this progress in understanding anatomy had not produced comparable results in understanding of physiology or in improvements in medical practice. The Spanish physicians, like their counterparts throughout Europe, practiced medicine according to principles laid down hundreds of years before by Arabic commentators on the works of Galen and Hippocrates. The writings of Rhazes and Avicenna dominated medical practice. The doctrine of the humors was used to explain illness and provided the rationale for every kind of treatment. The physicians could not really help much when confronted with sickness. They looked at a patient's urine and prescribed medications, most of which were ineffective. They bled their patients, and because many diseases get better spontaneously, they observed their patients' improvement and reaped the benefit from the natural course of illness. Surgery was primitive, and the doctrines of the purifying power of the red-hot iron for treating wounds, the laudable pus, and the healing by second intention of wounds were universally accepted.

On the other side of the Atlantic, the practice of medicine was not much different. We are well informed about Aztec medicine, thanks to the observations of Aztec society, culture, and civilization that were recorded by Spanish and native writers in the decades after the conquest. One of the most useful sources of this information is the treatise by Father Sahagún, written in Spanish and Nahuatl soon after the conquest of Mexico (Figure 1) and known as the Florentine codex.[1] A page is worth quoting[1(bk10,p30)]:

Figure 1.—The arrival of the Spaniards in the New World is depicted in the Florentine codex (original in Laurenziana Medicean Library, Florence, Italy). Note the many domesticated animals.

Figure 2.—A pre-Columbian skull (1100-1470 AD, Peru) shows 2 trephinations, 1 old and healed, 1 recent (Smithsonian Institution, Washington, DC).

> The good physician [is] a diagnostician, experienced—a knower of herbs, of stones, of trees, of roots. He has [results of] examinations, experience, prudence. [He is] moderate in his acts. He provides health, restores people, provides them splints, sets bones for them, purges them, gives emetics, gives them potions; he lances, he makes incisions in them, stitches them, revives them, envelopes them in ashes. The bad physician [is] a fraud, a half-hearted worker, a killer with his medicines, a giver of overdoses, an increaser [of sickness]; one who endangers others, who worsens sickness; who causes one to worsen. [He pretends to be] a counselor, advised, chaste. He bewitches; he is a sorcerer, a soothsayer, a caster of lots, a diagnostician by means of knots. He kills with his medicine; he increases [sickness]; he seduces women; he bewitches them.

Some of the native cultures in America achieved a notable degree of surgical skills. Trephination of the skull was widely practiced in many parts of the American continent (Figure 2). A study of skull specimens indicates that about 50% of the patients who had this particular operation survived the procedure and often lived long enough to have a second or third one. The mortality for a similar operation in Europe at that time was in the neighborhood of 80%.[2]

Of paramount importance in the understanding of the changes that took place after the conquest is a consideration of the religious practices of both societies. On the Spanish side, despite the greed, cruelty, and covetousness that were often manifested by the Conquistadores, their religious faith was impressively strong. They firmly believed that every event of human life—every victory, every defeat—was totally and absolutely the result of divine influence. The American societies not only shared this belief but went even further: All natural phenomena were controlled by deities who had to be propitiated and influenced on a daily basis to maintain human existence. The

Aztecs believed that when Huitzilopochtli, the Sun God, sank below the western horizon in the evening, he entered the underworld, and that human sacrifice was necessary to ensure that he could surmount the perils of the travel and would again emerge in the East the following day to provide warmth and light to his creatures.[3] This belief made the Aztecs engage in constant warfare with their neighbors to ensure a steady supply of captive victims for the purpose of sacrifice.

Demographic Catastrophe in America

The arrival of the Europeans in America started a process of a decrease of the native population unparalleled in human history (Figure 3). While the population figures for the American continent before the arrival of Columbus are understandably imprecise, scholarly work by S. F. Cook, W. W. Borah, H. F. Dobyns, and others has substantially increased the population estimates for that time.[4,5] Pre-Columbian population estimates have ranged from 8.4 to 112 million people. A currently accepted figure is 54 million.[6] After the Spaniards arrived, the records of baptisms, taxes, and specific attempts to count the population provide much firmer figures, and the dramatic decrease of the native population can be more accurately documented. For example, in 1492 when the Spaniards arrived on the island of Hispaniola, the population has been estimated at between 100,000 and 3 million people. Just 48 years later, only 240 natives were left alive. In New Spain (now Mexico) in 1519, before the arrival of Hernán Cortés, the population was somewhere between 5 and 25 million. By 1605, there was only 1 million left. We should never forget that behind all these cold statistics was a tremendous amount of suffering and anguish, as the Amerindians saw their societies collapse into total chaos, old values not only challenged but destroyed, and a new social order established.

The indigenous population of the New World decreased by at least 90% as the result of the Columbian encounter.[6] In 1650, the entire American continent contained only 5 million natives. This demographic catastrophe continued for three more centuries in the isolated parts of the American continent, although for the continent as a whole, the nadir of Amerindian population occurred around 1650.

An episode in the 19th century illustrates the magnitude of the tragedy: On June 19, 1837, the steamboat *St Peter's* arrived at the Mandan tribe villages in the Dakota territory. There were persons with smallpox aboard. A few days later, the first tribal victims were recorded. Within a few months the Mandan population had declined from 2,000 to 130![7] Among the dead was Chief Four Bears who had been painted by George Catlin in a famous portrait that is now at the Smithsonian Institution.

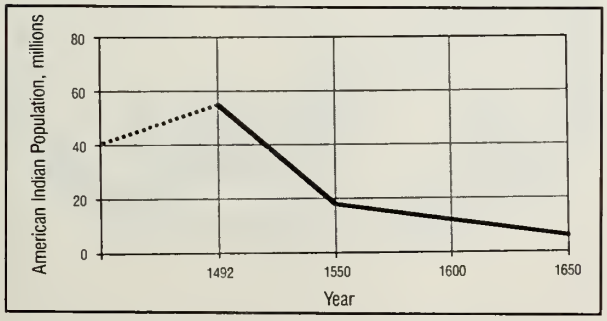

Figure 3.—The graph shows the estimated American Indian population before and after the Europeans arrived.

Figure 4.—Aztec Indians sick and dying during the first smallpox epidemic in Mexico are depicted in the Florentine codex.

Causes of Depopulation

After Columbus arrived from his second voyage in 1493, an outbreak occurred of a highly infectious febrile illness with respiratory tract symptoms that killed many thousands in Hispaniola and then spread to Cuba, Jamaica, and other Caribbean islands. In 1518 another destroyer, smallpox, arrived. It killed thousands in Cuba, moved to the mainland of North America in 1519, and killed millions there. The arrival of smallpox is well documented in the chronicles of the Conquest. After Cortés landed in Mexico, moved to the interior, and entered the Aztec capital of Tenochtitlan, another Spanish expedition headed by Cortés's rival, Pánfilio de Narvaez, arrived at the Caribbean coast of Mexico from Cuba. An African slave in that expedition had smallpox. The disease spread among the Indians like wildfire, killing thousands.[8] When it arrived at Tenochtitlan, the revolt against the Spaniards had already started. As Cortés and his men were forced to abandon the capital of the Aztec Empire in June of 1520, the Indian defenders, decimated by the epidemic and having lost to smallpox their chief, Cuitlahuac, were unable to pursue the invaders. This allowed the Spaniards time to reorganize, obtain reinforcements and supplies, and return to Tenochtitlan to finally conquer it in 1521.

The Indian chroniclers described the havoc caused by the disease in most poignant phrases (Figure 4)[1(bk12,p81)]:

And [even] before the Spaniards had risen against us, a pestilence first came to be prevalent: the smallpox. It was [the month of] Tepeilhuitl when it began, and it spread over the people as great destruction. Some it quite covered [with pustules] on all parts—their faces, their heads, their breasts, etc. There was great havoc. Many died of it. They could not walk; they only lay in their resting places and beds. They could not move; they could not change position, nor lie on one side nor face down, nor on their backs. And if they stirred, much they did cry out. Great was

TABLE 1.—*The Principal Diseases That Came to America From Europe or Africa*

Smallpox	Diphtheria	Measles
Whooping cough	Influenza	Typhoid fever
Yellow fever	Cholera	Malaria

its destruction. Covered, mantled with pustules, very many people died of them. And very many starved; there was death from hunger, [for] none could take care of [the sick]; nothing could be done for them.

The epidemic then moved south, devastating Central America. By 1524 it had arrived at the northern border of the Inca Empire in what is now Ecuador. There it killed the Inca emperor, Huayna Capac, and his designated successor, Ninan Cuyoche.[8] A civil war ensued with the armies of two aspiring rulers, Atahualpa and Huáscar, fighting each other. This fratricidal strife enabled Pizarro and his handful of men to conquer the mighty Inca empire in less than a year.

The smallpox epidemic may have killed as many as 30% of the population of the Aztec and Incan empires. But that was only the beginning. Recurrent epidemics, probably of measles initially, took place in 1531 and 1546. Influenza, typhus, mumps, and other diseases (Table 1) followed. By 1550 the conquered parts of America had become subject to the world epidemic cycle. Thus in 1556, an epidemic of a respiratory tract infectious disease, probably influenza, broke out in Europe and two years later arrived in America. As the European conquerors and their domesticated animals moved farther into the American continent, the cycle of repeated epidemics followed, devastating populations who had thus far been spared.[9] After the French established a colony at Port Royale in what is present-day Nova Scotia, an epidemic devastated the population of Massachusetts Bay from 1617 to 1620. This depopulation of the area opened the way for the arrival of the Pilgrims in 1620.[7]

There were, of course, cultural differences among European countries in their attitude toward the depopulation of America. Many times during his reign, Charles V decried the death of so many Indians and instructed the Council of Indies to pass laws that would soften their hardships. The Spaniards wanted the Indians to live so that they could benefit from their labor. English colonization was different; the settlers wanted the land for themselves. A poignant example of this attitude is the royal patent for the Plymouth colony in 1620 given by James I of England[10(p208)]:

Within this late yeares there hath by God's Visitation raigned a Wonderfull Plague . . . to the utter Destruction, Devastacion and Depopulation of the whole Territorye, so that there is not left for many Leagues together in a Manner that doe claim or challenge. . . . Whereby We in our Judgement are persuaded and satisfied that the appointed Time is come in which the Almighty God in his great Goodness and Bountie towards Us and our People hath thought fitt and determined that those large and goodly Territoryes, deserted as it were by their naturall inhabitants should be possessed and enjoyed.

As a result of the tremendous mortality caused by the epidemics among the American Indians, an inordinate degree of social disorganization took place. Crops were not cultivated, and villages often became leaderless as the chiefs or caciques died. In Mexico, the chroniclers of the Conquest inform us that Cortés was often able to appoint new chiefs, arbitrate land disputes, and in general, manipulate the situation in such a manner as to gain ultimate control. The Indians marveled at how the Spaniards were spared by the smallpox and other epidemics. It is likely that they thought this to be the result of divine intervention, which would explain the rapid conversion to Christianity that occurred among so many millions of natives of the Western Hemisphere soon after the conquest. The reasoning was simple: The gods are sending these epidemics, and only the Indians are afflicted and die. The Indians would have had to conclude that the Spanish gods were superior, and subsequently they converted en masse.[11]

Reasons for the Dramatic Differences in the Resistance to Acute Infectious Disease Epidemics

Since at least the time of the Roman Empire, trade routes made the transmission of disease possible across the entire length and breadth of Asia, Europe, and Africa. The map in Figure 5 shows the basic unity of the Old World, with Asia, Africa, and Europe forming a gigantic system for the exchange of pathogens and disease vectors. The slave trade from sub-Saharan Africa to the Islamic centers of North Africa had existed for many centuries before Columbus. For at least 200 years, small groups of African slaves had been arriving in southern Europe. The Silk Route linked China with the eastern Mediterranean, and exchanges of goods and people had been taking place for millennia in the Mediterranean basin and the European continent. Spain and Portugal were at the end of many of these routes. At the time of the conquest, most adult Europeans and their slaves had already had exposure to smallpox and were therefore immune to it. Ruy Diaz de Isla, a Spanish physician, noted as remarkable that he had once seen a Spaniard who had smallpox at the age of 20.[12] Measles and other highly infectious viral and bacterial diseases were also rampant in Europe, and peo-

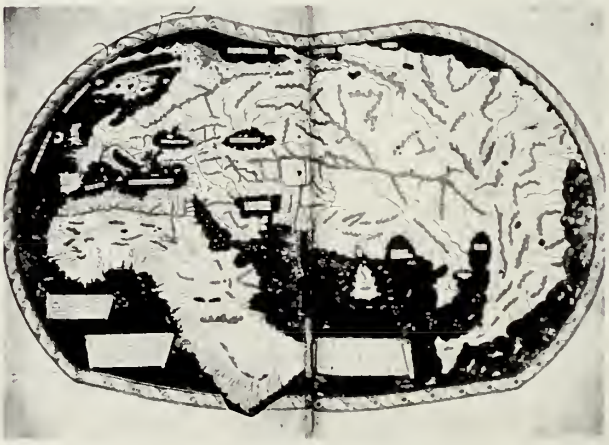

Figure 5.—Henricus Martellus's map of the world, circa 1489, shows the unity of Africa, Europe, and Asia (original in British Library, London, England).

ple were infected with them most often in childhood. Those who did not die recovered with permanent immunity. Such was the case for most of the Conquistadores who arrived on the American continent.

The American Indians, on the other hand, did not have any individually acquired or genetic natural resistance to smallpox, measles, yellow fever, malaria, or other imported infectious diseases. Over the course of many generations, repeated exposure to a particular microorganism results in a population of persons whose genetic makeup confers some protection against that particular pathogen. The American Indians had been isolated for millennia from the recurring pandemics that swept the Eurasian land mass and had not had the opportunity to acquire any resistance to these infections, many of which—like the measles virus that evolved from the virus that causes rinderpest in cattle and smallpox from cowpox—were derived from diseases of the domesticated animals of the Old World. Other infections are shared by humans and their domesticated animals. The absence of domesticated animals in America kept the natives protected from these infections, but rendered them highly susceptible when exposure took place.[11]

It is interesting to contrast the effects of the conquest of America with that of the Philippines by the Spanish, which also took place in the 16th century. The aborigines in the Philippines, like the American Indians, suffered exploitation and deprivation as a result of the European conquest, but there was far less depopulation in the Philippines. The difference lies in the thousands of years of isolation of humans in the Western Hemisphere compared with the steady contact that existed between the Asian mainland and the Philippine Islands. The Filipinos did not suffer the unique immunologic naiveté of the American Indians.

Another factor in the devastating effect of the imported infectious diseases on the American Indians was their relative lack of genetic diversity. Studies of immune system polymorphism have shown that Amerindians have a decreased number of alleles for histocompatibility antigens when compared with Old World populations. This results in a facilitated adaptation of infectious viruses and other microorganisms and thus in increased virulence as the pathogen passes to a genetically similar new host.[13]

Malaria

Another disease that was transmitted to America with incalculable health consequences was malaria. Although there has been debate in the past as to whether this was a disease originally present in the New World or imported from the Old World, the evidence today is incontestable. It is now known that malaria originated in Africa and was transferred from that continent to America, in all likelihood as a result of the slave trade. The historical evidence is helpful; malaria was well known in the Old World from remote antiquity. It had been described many times by classical Greek and Roman observers, and it had been rampant in Africa and the warmer latitudes of Europe for many centuries. In the New World there are no valid historical records pointing to the existence of malaria before the Europeans arrived. In fact, in the tropical areas of the Caribbean, the coast of the Yucatán peninsula, and the interior of South America (Amazonian basin), there were large and healthy populations with no evidence of having been weakened by chronic malarial infestation. In 1541, fifty Spaniards spent eight months in the Amazonian jungles, having left Quito (now Ecuador) to explore the eastern slopes of the Andes. Their adventure was carefully recorded by a friar, Gaspar de Carvajal. When they finally exited to the Atlantic Ocean, having traversed the South American continent by following the Amazon River to its mouth, ten men had died. Three were killed by the Indians, and seven died of starvation, but no mention of any fever was made although mosquitoes were extremely abundant. The shores of the Amazon River were found to be heavily populated, with many towns described and their inhabitants apparently in excellent physical condition. A century later, two Spanish priests made a similar journey with a large party, and the descriptions are almost identical.[12] By the end of the 18th century, this situation had completely changed. It was virtually impossible to penetrate the Amazonian basin or to travel in the hot and humid areas of the Caribbean for any length of time without contracting malaria.

Genetic evidence indicates that no American Indian group had ever achieved any substantial degree of natural protection against malaria. In the Old World, several genetic abnormalities had evolved that confer partial protection against malaria. Well-known examples include the association of hemoglobin S with resistance to falciparum malaria, as well as the protective effect of thalassemia and of glucose-6-phosphate dehydrogenase deficiency. It has also been known for at least 60 years that black Americans have a notable degree of natural resistance against *Plasmodium vivax* infection.[14] This is because the attachment of merozoites is mediated by specific erythrocyte surface receptors that are related to the Duffy blood group antigen Fy^a or Fy^b.[15] Many black Americans are descended from West Africans who lack these antigens and hence have resistance to *P vivax* malaria.

There are more than 50 species of malaria parasites and several hundred species of mammalian hosts. Analysis of the few plasmodia species that infect New World monkeys has shown extraordinary identity between them and the human parasites, making it virtually impossible that the two sets of parasites were the result of separate evolutionary convergence.[16] The few plasmodia present in the Western Hemisphere were recently imported, and the evidence almost unequivocally points to Africa as their origin. Receptive anopheline species were, of course, present in America and were able to maintain the life cycle of the parasite.

Yellow Fever

Another mosquito-transmitted tropical disease that was imported to America was yellow fever. Given the mode of transmission of this virus, the disease could not spread until the specialized mosquito that transports the

virus from one host to another could itself be transported to America and establish its place in the American ecology. This probably happened in the first half of the 17th century. *Aedes aegypti* is a highly domesticated mosquito that breeds almost exclusively in small puddles of stagnant water. Most likely it traveled in a slave ship from Africa in water casks. Once the mosquito had adapted to the American environment and had multiplied, yellow fever could strike, and indeed, the first recorded epidemic occurred in 1643 in the Caribbean area.[17]

Malaria and yellow fever arrived from Africa late after the initial conquest. Both diseases infected Europeans and American Indians alike. But the effect on the native population, which had been almost obliterated by a century of new acute infectious diseases with a high mortality, was devastating. In the hot tropical areas of America such as the Caribbean islands, the Yucatán coast, parts of Central America, the Pacific coast of Colombia and the Amazonian basin, the overwhelming majority of the American Indian population perished. Many Caribbean islands became totally devoid of American Indians. Because these were the areas where cheap labor was necessary for the sugar and cotton plantations, new labor had to be imported from Africa. The slave trade, which had begun soon after the conquest, grew even more. At least 10 million Africans were forcibly transported to the American continent until 1870, when the slave trade was finally abolished. The irony is that America provided some of the stimulus for the slave trade in terms of new food items that improved the nutrition of African populations and stimulated their replenishment at a time when large numbers of Africans were being sold into slavery to the traders on the coast of Guinea. I am referring to the importation of corn (maize) and manioc (cassava), two American crops, to Africa.

Figure 6.—A pre-Columbian Moche ceramic (100-750 AD, Peru) shows a probable facial bone tumor (Smithsonian Institution, Washington, DC).

Given the enormous devastation that European and African diseases caused in the original inhabitants of America, it is no wonder that a feeling arose among many survivors that before the arrival of the Europeans, America was an earthly paradise, free of disease. Thus the Mayan book *Chilam Balam*, written soon after the conquest, describes the pre-Columbian era in these terms[8(p36)]:

> There was then no sickness, no aching bones, no high fever, no smallpox, no burning chest, no abdominal pains, no consumption, no headache. At that time the course of humanity was orderly. The foreigners made it otherwise when they arrived here. They brought shameful things when they came.

Bad as these events were, this statement was not entirely true. There were many diseases among the American Indians before the European conquest. Given the lack of written language among pre-Columbian American native societies (with the exception of the Mayans), it is difficult to ascertain the history of diseases and epidemics before Columbus. But analyses of skeletal remains show the unmistakable presence of arthritis, bone tumors, Pott's disease, and treponemal diseases such as yaws and syphilis.[18] Some of the more advanced Indian societies left clear depictions of disease in their ceramics, including those of Bell's palsy, facial tumors (Figure 6), probable visceral leishmaniasis, and Peruvian verruca. Analyses of fossilized human fecal material have revealed the presence of multiple intestinal parasites in pre-Columbian times.[19] Clear evidence of the presence of miliary tuberculosis was found in the well-preserved mummified remains of a child from the Nazca desert of southern Peru,[20] and more recently, *Mycobacterium tuberculosis* DNA was demonstrated in another pre-Columbian Peruvian mummy.[21]

Origin of Syphilis

Given the remarkable constellation of killing diseases that came to America from the Old World, it is fair to ask what was taken back in return. There has been only one controversial candidate for the past 500 years, and the debate continues. The disease we know as syphilis has been thought to have appeared for the first time in Europe during the Italian wars of the late 15th century. At the siege of Naples in 1495 the army of the French king, Charles VIII, first encountered what was to the physicians of the time a new disease. This disease was characterized by genital ulcerations, a severe skin rash accompanied by agonizing pain in the arms and legs, and severe physical deterioration, often culminating in death. As the French army withdrew from Naples in the spring of 1495 with prostitutes and camp followers in its wake, the disease spread throughout northern Italy and then over the entire European continent. It was given different names: the Neapolitan disease, the French disease, the Spanish pox, and others. The most common name was the French disease or *Morbus gallicus*. Spanish chroniclers like las Casas and Oviedo unequivocally declared that the French disease had been brought to Europe by Spanish sailors who had acquired it in the Caribbean islands during the Columbian voyages. This view was supported by the pub-

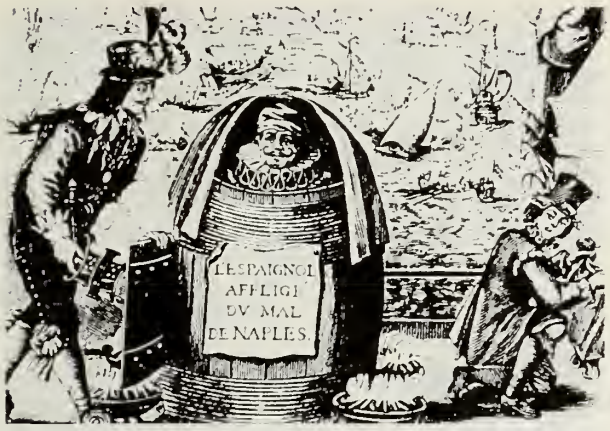

Figure 7.—An early 16th-century cartoon shows heat therapy being used for the treatment of syphilis (original in Bettman Archive, New York, NY).

lication in 1539 by Ruy Diaz de Isla of a book on the disease in which he stated that he had personally treated Spanish sailors returning from America with the French disease in 1493 in Barcelona.[8] The disease received its current name in 1530 when Fracastorius published the Latin poem, "*Syphilis sive Morbus gallicus*" ("syphilis or the French disease").

The debate as to the origins of syphilis has never ceased. In favor of the American origin is the fact that, until recently, no ancient skeletons had ever been unearthed in the Old World in which unequivocal bone syphilitic lesions were present. This was the case despite extensive examination of thousands of Egyptian mummies and hundreds of European pre-Columbian skeletons.[22] On the other hand, many American pre-Columbian skeletal remains have shown evidence of bone treponemal disease.[18,22] More recently, however, a few skeletons with what appear to be bone syphilitic lesions have been found in tombs that preceded the Columbian encounter in a Greek colony in Italy[23] and in England. The debate as to the origin of syphilis may well be moot because there is increasing evidence that all four of the treponemal diseases—syphilis, endemic syphilis or bejel, yaws, and pinta—are all caused by the same treponeme.[24,25] If this is so, these treponemal infections were likely present in humans on both sides of the Atlantic at the time of Columbus's trip.

The syphilis epidemic in the early 1500s touched all levels of society; kings, emperors, cardinals, popes, and the poorest of the poor were afflicted.[8] Famous humanists like Erasmus and Ulrich von Hutten wrote about it. Desperate attempts were made to find an effective treatment. An infusion from the bark of the guaiacum tree, an American tree, was thought to provide a cure, only to disappoint everybody a few decades later. Mercury was used with some benefit. The prices of these drugs escalated so much that physicians were called alchemists because they could transform mercury into gold! That syphilis abated following fever was noted in 1539 by Ruy Diaz de Isla,[8] and hot baths became common (Figure 7). This observation was confirmed 400 years later in 1927 when Julius Wagner von Jauregg from Austria was awarded the Nobel prize in medicine for his discovery of the beneficial effects of inducing fever by inoculating malaria in patients with tertiary syphilis.

TABLE 2.—*A Partial List of the Food Plants Provided by America to the World*

Corn (maize)	Peppers	Avocado
Potato	Squashes	Pineapple
Sweet potato	Manioc (cassava)	Papaya
Beans	Tomato	Vanilla

Nutrition and the New World

One of the most important biologic consequences of the arrival of the Europeans in America was their discovery and use of the many food plants that the American Indians had developed over several millennia. A partial list is given in Table 2. In all, American Indians domesticated more than 20 species of important food plants, a long process of trial and error that resulted in the development of the species that were to form the basis of the diet of most people in the world a few centuries later.

Without a knowledge of modern genetics, the American Indians domesticated many varieties of wild plants by a complex process that involved hybridization of different wild species, with a resulting multiplication of chromosomal sets (polyploidy). Such is the case of the potato, which is a tetraploid with 48 chromosomes. Developed thousands of years ago by the inhabitants of the high Andean plateaus of Peru and Bolivia, it was transplanted in the 16th century to Europe where it slowly gained acceptance. It offered the advantage of a higher volume of production and caloric content per acre of cultivated land than rye or other food sources of northern Europe. Furthermore, because potatoes grew in the ground, they became a reservoir of food that could not be easily stolen by soldiers during war or easily requisitioned by rulers. By the end of the 18th century, potato use was widespread in northern Europe.[26] Soon thereafter, it became the staple

Figure 8.—Vincent van Gogh's *The Potato Eaters* (1885) is shown. At the time, this was a common daily scene across northern Europe (original in Rijksmuseum Vincent van Gogh, Amsterdam, The Netherlands).

food of large segments of the European population (Figure 8).

Corn (maize) was the most important food item in the diet of Americans and played a major role in their art, religion, and rituals. Columbus took it to Europe on returning from his first voyage. It rapidly spread throughout Europe, Africa, and Asia, becoming an important food in the diet of humans and also of domesticated animals. American food crops rapidly traveled around the world, spreading as far away as China, where by the end of the 16th century, peanuts, sweet potatoes, and corn were extensively cultivated. Sweet potatoes were to become an important component of the daily caloric content of the Chinese diet. In Africa, the cultivation of manioc (cassava), which was transplanted from its native Brazil in the 16th century, became widespread and provided one of the most important foods in the African diet for centuries to come.[8]

These new American foods resulted in a substantial growth of the populations of Europe and Africa and, therefore, played an important role in the demographic exchanges that took place. As the American Indian population dramatically decreased because of the diseases imported from Europe and Africa, the American population was being replaced by immigrants from Europe and by African slaves.[27] This exchange of populations continued well into the 19th century. What role the imported American food crops played in the demographic explosion in China after the 16th century can only be conjectured, but it was undoubtedly important.

New World Ritual and Stimulating Plants

Several plants were grown by the original inhabitants of the Western Hemisphere for medicinal, ritual, or religious purposes. Among them are several that have acquired great importance both as a source of pleasure and as a cause of severe health problems. The first one is relatively harmless: *Theobroma cacao,* the source of chocolate, the beverage that Cortés found being widely used at Montezuma's court on his arrival at the capital of the Aztec Empire. Both the Aztecs and Mayans used cacao beans as a form of currency, which indicates the high esteem in which they held this stimulating item. The second one, *Erythroxylum coca,* grown from time immemorial in the high plateaus of the South American Andes and its leaves chewed by the Incas for the relief of fatigue and hunger, has, as is common knowledge, become a serious health problem around the world in the second half of the 20th century. There is a dramatic difference between the amount of cocaine that is absorbed when coca leaves are chewed and what happens after the production by western technology of the pure alkaloid of the plant and its ingestion in vastly higher amounts.

The third plant in this category that America gave to the world is, of course, tobacco. It was named *Nicotiana tabacum* in honor of Jean Nicot, the French ambassador to Lisbon, who in 1550 sent tobacco plants to Catherine de Medici in Paris. When Columbus first arrived in Cuba, his men observed the intermittent use of the leaves of this plant, which the natives rolled into cylinders and lit, inhaling the smoke through their noses.[28] Figure 9 shows a very early representation of smoking and is taken from the pre-Columbian Mayan book known as the Tro Cortesianus or Madrid codex. The use of this plant was ritualistic, sporadic, and limited to small amounts. The modern world has seen the use of tobacco multiplied a billion-fold—packed, wrapped, and aggressively marketed by a profit-hungry industry and now causing an estimated 450,000 deaths every year in the United States alone. The World Health Organization estimates that at least 750 million human beings will have their lives substantially shortened by the use of cigarettes. It can be appreciated then, that the Columbian encounter continues to have consequences, good and bad, intended and unintended, for the entire world.

Figure 9.—Tobacco smoking was depicted in pre-Columbian times (Codex Tro Cortesianus, 15th century; original in Museo de America, Madrid).

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Conferences and Reviews

Familial Benign Hypercalcemia—From Clinical Description to Molecular Genetics

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Familial benign hypercalcemia (or familial hypocalciuric hypercalcemia), a syndrome of lifelong hypercalcemia inherited as an autosomal dominant trait, is distinct from the multiple endocrine neoplasia syndromes and other forms of inherited parathyroid disease. Familial benign hypercalcemia results from the inappropriate secretion of parathyroid hormone despite hypercalcemia, enhanced renal tubular reabsorption of calcium (independent of parathyroid hormone), and apparent tissue resistance to adverse effects of hypercalcemia. Heterozygosity for the familial hypercalcemia trait is benign, although homozygosity for the trait may lead to severe neonatal primary hyperparathyroidism. Genetic linkage studies show that most persons affected with familial hypercalcemia have a mutation on the long arm of chromosome 3 (3cen–q21), although one phenotypically indistinguishable family appears to have a mutation on the short arm of chromosome 19 (19p), and another family has neither 3q nor 19p mutations. One group has recently shown mutations in a putative parathyroid cell-surface calcium receptor that are plausible causes for the chromosome 3q variant of the familial hypercalcemia syndrome. Perhaps the other genes for this syndrome encode proteins representing hitherto-unknown regulators of systemic calcium metabolism independent of parathyroid cell calcium sensing or proteins involved in signal transduction from the calcium receptor.

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In this article I give a brief overview of familial benign hypercalcemia (FBH),[1-4] which has also been reported as familial hypocalciuric hypercalcemia and hereditary hyperparathyroidism.[5,6] After a historical introduction, I summarize the abnormalities of the syndrome, review new data that establish the existence of at least three genetically distinct but phenotypically indistinguishable forms,[7] and outline recent evidence for specific mutations causing one form of FBH. This is not a comprehensive review; only selected articles are cited, and for some issues, detailed reviews cited will give access to the original citations.

Historical Background

The first family recognizable in the literature as having the familial benign hypercalcemia syndrome was a kindred reported in 1966 among seven families thought to have hereditary primary hyperparathyroidism.[5,8] This family had symptomless hypercalcemia without clear evidence of parathyroid hormone (PTH) hypersecretion.[8] Subtotal parathyroidectomy was unsuccessful in relieving the hypercalcemia, and it was suggested that the condition may be a new one.[8] In 1972 a second family with this syndrome was described, and the syndrome was named "familial benign hypercalcemia."[1] The essential features of the FBH syndrome were defined in that report, including hypercalcemia, mild hypophosphatemia, normal serum alkaline phosphatase levels, normal serum levels of immunoreactive parathyroid hormone, mild hypermagnesemia, the absence of hypercalciuria, and the failure of subtotal parathyroidectomy to return serum calcium levels to normal. In 1977 several families with the FBH syndrome were reported, and in recognition of the relatively low urinary calcium excretion, the term "familial hypocalciuric hypercalcemia" was devised.[6]

Since these initial descriptions, more than 50 families and over 250 affected persons have been described as having the FBH syndrome, and the clinical characteristics have been extensively validated.[1-4,9-12]

Clinical Characteristics

The features of FBH are compared and contrasted with those of sporadic and familial primary hyperparathyroidism in Table 1. Clinically, FBH is a bland syndrome that is almost always found serendipitously by serum calcium measurement. Although there is some disagreement,[2] our studies and those of others[3,4,10,11] suggest that what might appear to be symptoms of FBH result from

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ABBREVIATIONS USED IN TEXT

FBH = familial benign hypercalcemia
PCR = polymerase chain reaction
PTH = parathyroid hormone

ascertainment bias: probands seek medical care for some reason, and hypercalcemia is detected incidentally. Persons ascertained by screening have no more symptoms than their unaffected relatives.[3] A few reports suggest that FBH may cause recurrent acute pancreatitis, but this, too, may represent ascertainment bias artifact because physicians routinely test for hypercalcemia in patients with pancreatitis.[13] As described later, severe primary hyperparathyroidism of neonates may be an uncommon manifestation of FBH. Unlike patients with typical primary hyperparathyroidism, those affected with FBH do not have osteopenia,[14,15] hyposthenuria,[16] or other symptoms of hypercalcemia.[1,3,4,10,11] Nonetheless, having FBH can be a substantial health problem because it can masquerade as primary hyperparathyroidism so closely that it is totally indistinguishable with available tests.[4]

Renal Function in Familial Benign Hypercalcemia

The renal difficulties seen in patients with severe primary hyperparathyroidism are virtually absent in FBH. The glomerular filtration rate is well maintained into advanced age,[3] and maximal urinary concentrating ability is preserved in FBH versus the hyposthenuria that accompanies primary hyperparathyroidism.[16] Urinary excretion of cyclic adenosine monophosphate is generally normal in FBH, suggesting no excess action of PTH on the kidneys.[3,10]

The urinary excretion of calcium is virtually never elevated in patients with FBH. In our detailed studies of 21 families, 75% of affected family members excreted less than 2.5 mmol of calcium per day (100 mg per 24 hours) (average, 2.2 mmol per day).[3] Urinary calcium excretion may reach 6.2 mmol per day (250 mg per 24 hours), however.[2,3] One patient my group studied excreted 5.0 to 6.2 mmol of calcium per day (200 to 250 mg per 24 hours) and has had several episodes of calcium oxalate urolithiasis (unpublished results). Perhaps he has both FBH and idiopathic hypercalciuria. As noted earlier, even in the absence of PTH, there is enhanced renal tubular reabsorption of calcium (and magnesium) in patients with FBH, in comparison with persons inadvertently made hypoparathyroid after the removal of sporadic parathyroid adenomas.[4] Studies with diuretics and lithium suggest that the site of enhanced renal tubular calcium reabsorption is either the proximal nephron or the ascending limb of the loop of Henle.[4]

Abnormal Function of Parathyroid Glands

The hypercalcemia of FBH is not due to abnormal protein binding, as serum protein concentrations are normal and serum ionized calcium levels are elevated. Only a few persons have clinically overt hypophosphatemia, although in some it can be noteworthy. On average, the serum magnesium concentration in affected persons is at about the upper limit of normal. Generally, serum alkaline phosphatase activity is normal in FBH. Thus, the only biochemical sign of PTH excess in most patients is hypercalcemia.[1-4,9-12]

Initial data about serum immunoreactive PTH levels in FBH were widely discrepant (reviewed by Law and coworkers).[17] The exact reasons for the discrepancies are not

TABLE 1.—*Clinical and Biochemical Features of Sporadic and Familial Hyperparathyroidism (Primary HPT) Versus Familial Benign Hypercalcemia*

Variable	*Sporadic Primary HPT*	*Familial Primary HPT*	*Familial Benign Hypercalcemia*
Age of onset	Generally >40 years	Variable*	Birth
Serum or plasma level			
Calcium	Elevated	Elevated	Elevated
Magnesium	Variable	Variable	Normal to elevated
Inorganic phosphorus	Normal to very low†	Normal to very low†	Normal to mildly decreased
Calcitriol‡	Normal to elevated†	Normal to elevated†	Normal to slightly decreased
Intact parathyroid hormone	Increased§	Increased§	Normal‖
Urinary excretion			
Cyclic AMP	High normal to increased¶	High normal to increased¶	Normal to mildly increased
24-Hr calcium excretion	Variable#	Low to elevated	Normal to low**
Calcium clearance:creatinine clearance ratio	Usually >0.02††	Usually >0.02	Generally <0.01‡‡
Other findings	Occasional signs of hyperparathyroid bone disease, chondrocalcinosis, urolithiasis; enlarged parathyroid gland by ultrasonography	Occasional signs of hyperparathyroid bone disease, chondrocalcinosis, urolithiasis; enlarged parathyroid gland(s) by ultrasonography	Occasional chondrocalcinosis, possible gallstones

cyclic AMP = cyclic adenosine monophosphate

*The condition can appear as early as childhood to as late as midlife.
†Present in 50% of persons tested.
‡Calcitriol = 1,25-dihydroxyvitamin D.
§Hormone levels are increased in 80% to 90% of persons tested.
‖Intact parathyroid hormone levels are increased in 15% of persons tested.
¶Occurring in more than 75% of persons tested.
#Urinary calcium excretion is increased in 30% to 50% of persons tested.
**Excretion is <100 mg/day in 75% of persons tested.
††Occasionally the ratio is <0.01.
‡‡The ratio is almost never >0.02.

known, but the development of two-site immunometric assays for PTH has clarified things considerably. We measured PTH levels in the serum of FBH subjects by midregion radioimmunoassay, bioassay, and two different two-site immunometric assays, with remarkably similar findings.[18,19] Serum intact and bioactive PTH levels cluster in the lower half of the normal range for most persons having FBH, but some are in the upper half of the normal range, and 10% to 20% are mildly elevated. In contrast, serum PTH concentrations are unmistakably elevated in 80% to 90% of patients who have primary hyperparathyroidism.[18,19] The diagnostic approach to this difficult problem (elevated PTH levels in FBH) has been discussed elsewhere.[4]

The "normal" concentrations of serum PTH in most hypercalcemic patients with FBH are paradoxical and suggest a priori an abnormality of parathyroid gland function. Indeed, parathyroidectomy causes hypocalcemia in patients with FBH, establishing that the hypercalcemia is PTH-dependent. The relationship between the degree of calcemia and the level of serum PTH, however, differs from that in primary hyperparathyroidism (Figures 1 and 2). A positive linear relationship has been shown between serum calcium and serum intact PTH levels in persons with FBH, which had been known for a long time to be the case in primary hyperparathyroidism.[19] The relationships are different between the two diseases, however, both for serum calcium (Figure 1) and inorganic phosphorus (Figure 2). Primary hyperparathyroidism appears to be characterized by subnormal sensitivity to PTH, as would be expected from receptor internalization or desensitization in response to hormone excess. Relatively speaking, then, people with FBH are more sensitive to PTH than those with primary hyperparathyroidism. Tissue sensitivity to PTH is probably not actually increased in FBH.[4,19] Remarkably, serum levels of PTH are low in some patients with FBH,[18,19] consistent with the thought that excess PTH is not the sole cause of the hypercalcemia.

Alterations in the set point for the calcium suppression of PTH secretion have been described for cells derived from parathyroid adenomas.[20,21] We examined PTH suppressibility in normal volunteers, patients with FBH, and those with primary hyperparathyroidism (Figure 3).[22] Calcium infusion that raised serum calcium levels identically in the three groups fully suppressed PTH levels in those with FBH, but suppression was incomplete in patients with primary hyperparathyroidism. Log transformation of the data (Figure 4) demonstrates more clearly the rightward shift of the calcium:PTH secretion dose-response curve in FBH, but with no change in slope or in final achieved PTH levels. In contrast, patients with hyperparathyroidism had both a rightward shift of the dose-response curve and variable degrees of PTH nonsuppressibility that were related to tumor mass.[22]

Neonates in FBH families rarely may have unusual parathyroid abnormalities. Severe neonatal hyperparathyroidism with diffuse parathyroid hyperplasia has been reported to occur in children with one or both parents affected[23]; it is not clear if homozygosity for the FBH trait is always required for neonatal hyperparathyroidism to occur. This is in contrast to normal or mildly hyperplastic parathyroid tissue found in adults with FBH.[2,3] Many af-

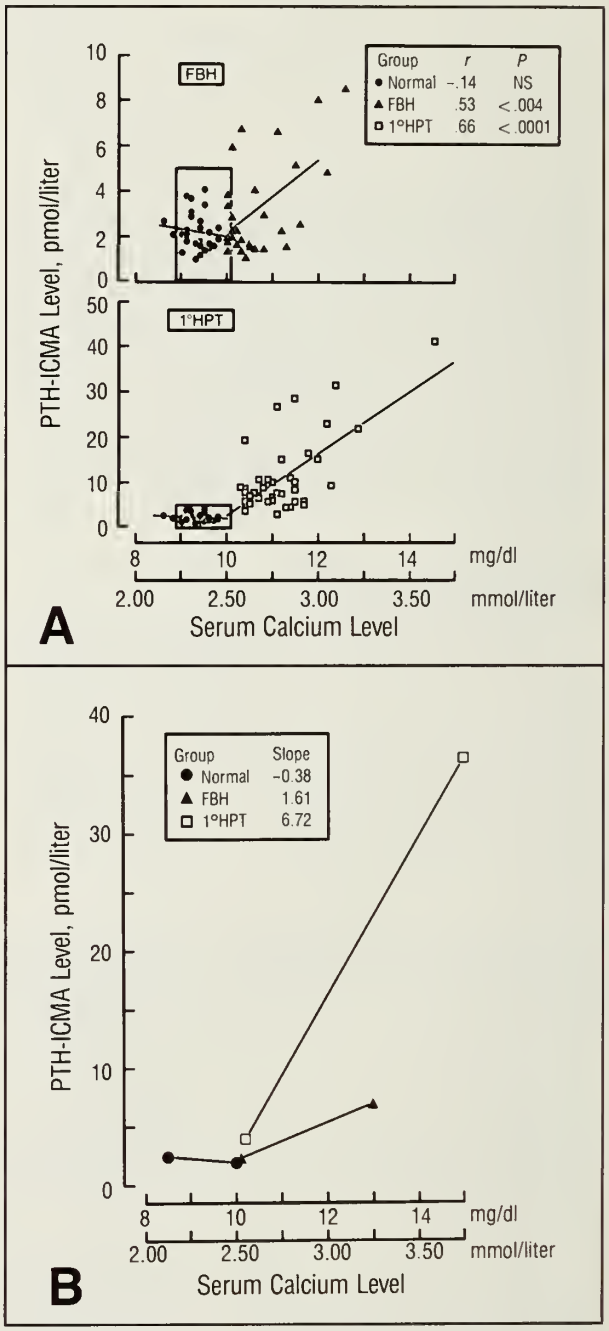

Figure 1.—Plasma intact parathyroid hormone levels by immunochemiluminometric assay (PTH-ICMA) as a function of serum calcium levels are shown in normal controls, patients with familial benign hypercalcemia (FBH), and patients with primary hyperparathyroidism (1°HPT). A, The upper panel shows data for normal controls contrasted with data for those with FBH; the lower panel contrasts data from patients with 1°HPT with data from normal controls (note different vertical scales). B, Regression lines for all three data sets are shown on the same scale. The boxes in panel A represent limits of normal values (from Firek et al[19]). NS = not significant

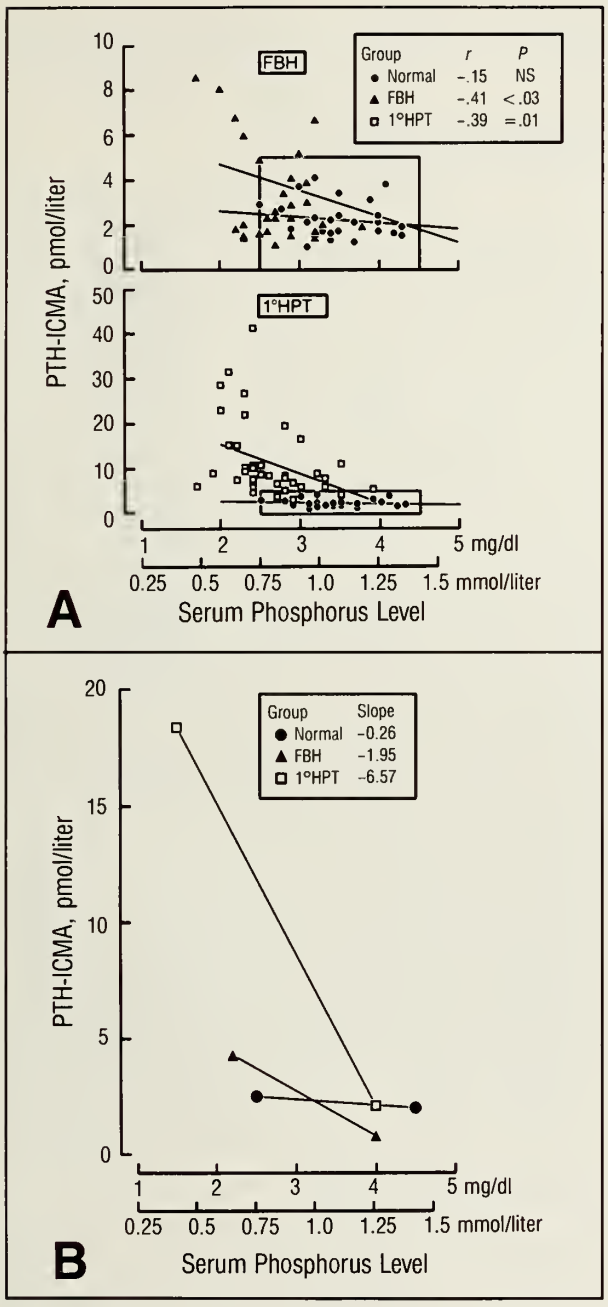

Figure 2.—Plasma intact parathyroid hormone levels by immunochemiluminometric assay (PTH-ICMA) are shown as a function of serum inorganic phosphorus in normal controls and subjects with familial benign hypercalcemia (FBH) and primary hyperparathyroidism (1°HPT). Symbols and overall layout are the same as in Figure 1 (from Firek et al[19]).

fected with neonatal severe primary hyperparathyroidism who also have FBH have been treated with subtotal parathyroidectomy, but the infants may recover with conservative therapy.[24,25] In contrast, unaffected babies of women with FBH may suffer prolonged hypocalcemia.[26]

Unifying Pathophysiologic Hypothesis

From the studies of renal and parathyroid function in FBH, it appears that affected persons have at least two de-

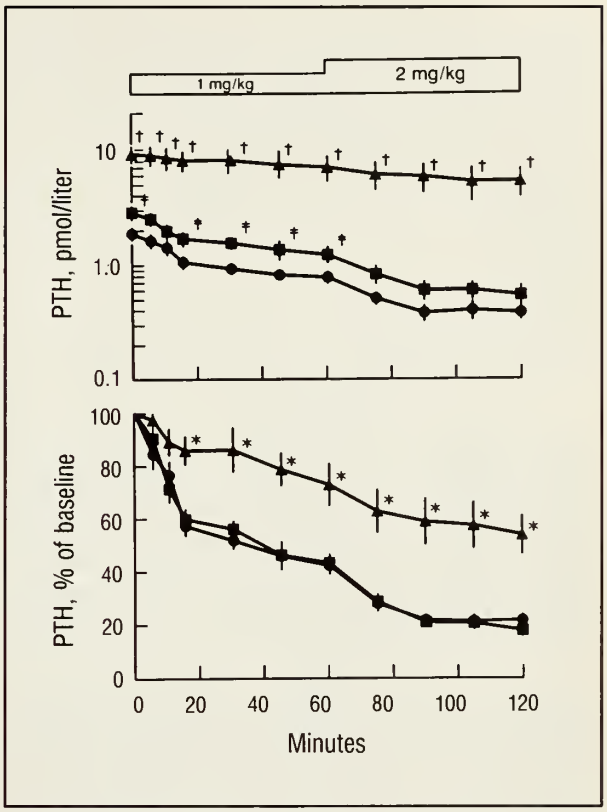

Figure 3.—Changes in plasma intact parathyroid hormone (PTH) levels are shown as a function of time during calcium infusion in normal control subjects (•), patients with familial benign hypercalcemia (FBH, ▪), and patients with primary hyperparathyroidism (1°HPT, ▲). The top panel shows the absolute concentration of PTH versus time; in the bottom panel, PTH is expressed as a percentage of the basal or initial concentration. * = $P < .001$, HPT versus normal controls or FBH; † = $P < .005$, HPT versus normal controls or FBH; ‡ = $P < .05$, FBH versus normal controls. The vertical lines represent ±1 standard error of the mean. The calcium infusion rate is depicted at the top of the figure (from Khosla et al[22]).

fects, a persistence of normal PTH secretion in the face of hypercalcemia and PTH-independent, enhanced renal tubular reabsorption of calcium. What single genetic mutation could result in these two abnormalities? New evidence, reviewed in the following sections, suggests that an integral plasma membrane protein common to the two organs is involved in calcium sensing, calcium transport, or both, and that one of several mutations in that gene may be related to one form of FBH.*

Epidemiology and Genetics

The incidence and prevalence of FBH are unknown. As reported from the National Institutes of Health, 9% of patients referred after failed neck explorations for suspected primary hyperparathyroidism had FBH.[27] Probably fewer than 30% of all patients with primary hyperparathyroidism undergo surgical therapy,[28] and of those who do, more than 90% are cured after one operation.

*See also the editorial by G. J. Strewler, MD, "Familial Benign Hypocalciuric Hypercalcemia—From the Clinic to the Calcium Sensor," on pages 579-580 of this issue.

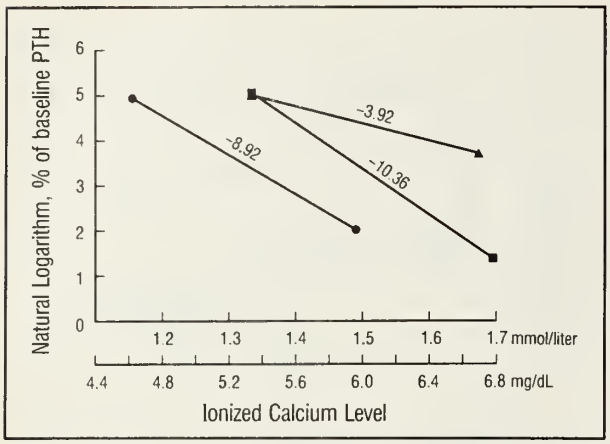

Figure 4.—Relationship is shown between the natural logarithm of the percentage of baseline parathyroid hormone (PTH), and ionized calcium in normal subjects (●) and in patients with familial benign hypercalcemia (FBH, ■), and primary hyperparathyroidism (1°HPT, ▲). Numbers are the slopes of the respective regression lines. The *P* values for comparisons of the slopes are as follows: normal versus FBH, .357; normal versus 1°HPT, .004; FBH versus 1°HPT, .001 (from Khosla et al[22]).

Furthermore, only a minority of patients with hyperparathyroidism are referred to a major center like the National Institutes of Health, resulting in substantial referral bias. For example, major centers are more likely to receive patients who have had more than one failed neck exploration or who have some other unusual problem.[27] Thus, patients with FBH must constitute only a tiny fraction of all patients with hypercalcemia. Because the disorder is essentially asymptomatic, it is seldom detected except incidentally or in family screening, making it difficult to know the actual prevalence. Because the trait is essentially harmless to reproductive capacity and survival, there would appear to be no major adverse selection pressure on patients carrying the FBH gene, and the trait might therefore become increasingly common.

All observers agree that the pattern of FBH in families suggests autosomal dominant inheritance with essentially complete penetrance (example of pedigree in Figure 5). Some clinical observations have suggested that there is a notable excess of affected persons in the kindreds.[2,3,10] This impression was probably created by difficulties with blood sampling and interpretation of serum calcium values in earlier studies. Blood specimens have often been taken under uncontrolled circumstances in local hospital laboratories or private physicians' offices and mailed to the investigating centers. There was no way for the investigators to exclude tourniquet stasis, for example, which falsely elevates serum total calcium values. Furthermore, many of the family groups in which an excess number of affected persons appeared represented infants and juveniles. Hypercalcemia was likely diagnosed in some young patients without the higher normal range for serum calcium levels in children than in adults being taken into account.[29] In recent studies for which affection status (diagnoses) was extensively validated, 46.4% were affected, 47.9% were unaffected, and 5.7% were unclassifiable in families at risk.[7,30] These data suggest that simple autosomal dominant inheritance exists without any effect of the FBH trait on implantation, development, or delivery.

Genetic Linkage Analysis in Familial Benign Hypercalcemia

A few years ago, further pathophysiologic studies in patients or readily accessible tissues[31,32] seemed unlikely to determine quickly the molecular basis of the FBH syndrome. For this reason, several groups began using modern techniques of genetic linkage analysis[33,34] for a "reverse genetics" or "positional cloning" approach to finding the gene mutated in FBH. Underlying genetic linkage analysis is the principle of genetic recombination during meiosis.[35] Modern genetic linkage analysis requires preparing leukocyte DNA from as many members of as many families as possible, firmly establishing the affection status in each person (affected, unaffected, or unknown), and using the DNA to trace inheritance of polymorphic alleles that are known to reside at specific chromosomal locations. Coinheritance of a given polymorphic allele with the disease trait establishes a statistical probability of physical continuity between the marker locus and the mutated gene responsible for the disease.[33-35] Polymorphic alleles can be detected as restriction fragment length polymorphisms, the most highly polymorphic of which are called variable-number tandem repeats. The newest and most powerful tool in the linkage armamentarium, however, is the detection of highly polymorphic dinucleotide, trinucleotide, or tetranucleotide repeat sequences—such as $(CA)_n$, $(AAAG)_n$, and $(AGAT)_n$—by selective amplification of sequence-tagged sites using the polymerase chain reaction (PCR).[36] The sequence-tagged sites are mapped to specific loci[37,38]; PCR primers are constructed to flank the polymorphic sequences, and radioactive products are separated on large polyacrylamide gels for radioautography and scoring. Some PCR-based polymorphisms manifest more than 20 alleles and a high prevalence of heterozygosity, greatly increasing the power of linkage analysis. The use of PCR also decreases by orders of magnitude the amount of DNA needed for linkage studies.

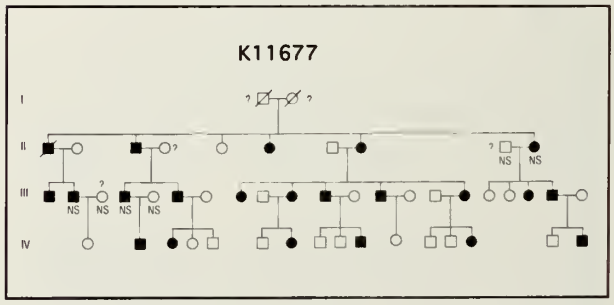

Figure 5.—A pedigree is shown for a representative large family having familial benign hypercalcemia in which the trait was mapped to chromosome 3q (from Heath et al[7]). The squares denote males, the circles females. Filled symbols denote persons affected with the disorder, and a diagonal line indicates that the person is deceased. NS = not sampled, ? = affection status unknown

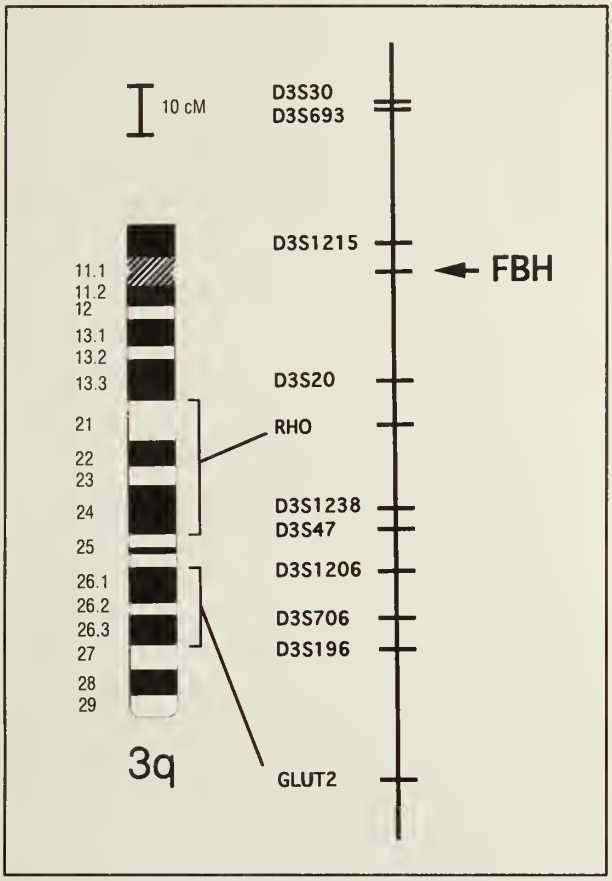

Figure 6.—The schematic diagram shows chromosome 3, with the genetic map showing the relative location of markers linked to the phenotype for familial benign hypercalcemia (FBH_{3q}) in 4 families and the calculated placement of the FBH locus (arrow). Note that the bulk of the short arm is omitted from the diagram. Distances between the markers are in centimorgans (cMs; recombination units). The numbers at the left represent band numbers on the chromosomal ideogram, and the numbers at the right signify names of specific marker loci, such as D3S30, RHO (from Heath et al[7]).

With the use of such techniques, several candidate genes were excluded from responsibility for FBH, such as the loci for multiple endocrine neoplasia types 1 and 2, PTH, and PTH-related peptide.[30] Other random loci had been excluded earlier by others (reviewed by Heath and Leppert).[30] More recently, a general linkage search was conducted in which the genome was screened for cosegregation of the FBH trait and numerous polymorphic markers.[39] In four unrelated families, a high probability was established that the gene mutated in FBH families resided on the long arm (q) of chromosome 3 at the position designated 3q21–q24 (bands 21 to 24 of the long arm). In studies of five different families,[7] my group confirmed that the FBH trait cosegregated with markers on chromosome 3q in four. The chromosomal location 3cen–q21—the trait lying somewhere between the centromere (cen) and band 21 on the long arm of chromosome 3 (Figure 6)—was more centromeric than reported previously.[39] To our surprise, we also demonstrated that in a single family, the FBH trait was closely linked with markers on the short arm (p) of chromosome 19.[7] This 19p family was phenotypically indistinguishable from the other families, except that they had milder hypercalcemia than all but one of the 3q families. Since the publication under discussion,[7] we have examined many additional families and have found the FBH trait linked only to chromosome 3q markers (unpublished results). Moreover, linkage of the FBH trait to markers on chromosome 3q has been reported in three more families.[40] In a report in abstract form, a family with FBH was evaluated in whom there was linkage to neither 3q nor 19p markers, suggesting that there are at least three genetically distinct forms of FBH, which I propose to designate as FBH_{3q}, FBH_{19p}, and FBH_0.[41]

Research may have uncovered the first specific mutations causing a form of FBH, the FBH_{3q} variant.[40] The complementary DNA for a putative bovine parathyroid cell-surface calcium receptor, which appears to be a G protein-coupled structure with seven transmembrane-spanning domains, was cloned.[42] Probes for the bovine receptor were used to screen three families thought to have FBH_{3q}, and three distinct mutations were found, two in what is thought to be the extracellular domain of the protein and one in the third intracellular loop.[40] The latter mutation was tested in vitro and affected the calcium-sensing function of the protein. The mutations were reported in three families not reported on previously,[39] so it is unclear if all FBH_{3q} families will have mutations in the same areas of the gene.

These new data are exciting for several reasons:

- It appears that most families showing the FBH phenotype have mutations at the same genetic locus and probably in the same gene.[7,39,40]
- The FBH_{3q} variant appears to result from mutations in a new regulatory protein that will be a fascinating subject for physiologic study.[43]
- Knowledge that there are three distinct mutations causing the FBH phenotype expands the scope of the inquiry considerably and suggests that there may be in addition to mutations in the parathyroid cell-calcium receptor[40] alterations in hitherto-unknown related calcium-sensing or calcium-transport proteins. Alternatively, perhaps the FBH_{19p} and FBH_0 mutations alter signal transduction mechanisms downstream from the parathyroid cell calcium receptor.
- Knowledge that the calcium receptor protein is expressed in renal tissue suggests a unifying explanation for the parathyroid and renal manifestations of FBH.[42]

There is a great need now to obtain specimens from all known FBH families so that their DNA may be incorporated into ongoing linkage and mutational analyses. More families with the FBH_{19p} and FBH_0 variants are needed for refinement of the chromosomal locations and eventual cloning of the mutated genes. Even small families unsuitable for linkage analysis should be sampled to determine the frequency and functional effects of various mutations. That there will be many additional allelic mutations for

FBH_{3q}, resulting in the variable clinical phenotype, seems likely. For example, perhaps only certain mutations can result in the severe neonatal hyperparathyroidism phenotype or in the relatively greater hypercalcemia some families manifest.[44]

The Future

In a little more than 20 years, we have gone from the incidental discovery of the FBH syndrome, through clinical description, to extensive pathophysiologic studies that identified the parathyroid glands and the kidneys as the sites of abnormal calcium metabolism, and now to the beginning of specific molecular explanations for the syndrome. The rapidly evolving technology of genetic linkage analysis, plus some good luck and intuitive pursuit of a candidate gene,[40] led to mutations in one form of FBH and to the approximate location of another gene that when mutated causes the clinical phenotype of FBH. Knowledge of the structures and functions of the FBH genes will provide substantial additional information about normal and deranged regulation of plasma calcium. It seems possible—perhaps even likely—that diseases less "benign" than FBH will be associated with other mutations of these genes.[43] For example, is it possible that mutations of the parathyroid cell calcium receptor could be involved in the pathogenesis of parathyroid neoplasms?

Addendum

Since this manuscript was submitted, a report has appeared supporting the concept that severe neonatal primary hyperparathyroidism in FBH_{3q} results from homozygosity for mutations in the parathyroid cell calcium receptor gene.[45] In addition, we have discovered three unique mutations of the calcium receptor gene (distinct from those reported earlier[40]) that co-segregate with the FBH_{3q} phenotype (H.H.H., S. Odelberg, D. Brown, et al, unpublished data, April 1994). Thus, of the six calcium receptor mutations so far found in FBH_{3q}, all are different.

Acknowledgment

Bill Law, Jr, MD, had major responsibility for creating the original clinical resource. Karen Laakso was study coordinator at a key period in the development of these studies. Mark Leppert, MD, Dora Stauffer, Brith Otterud, Virginia Hill, and Donna Brown provided patient and good-humored assistance with the genetic linkage studies. Finally, the author is deeply grateful for the selfless cooperation of the FBH family members.

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Epitomes

Important Advances in Clinical Medicine

Occupational Medicine

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in occupational medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in occupational medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Occupational Medicine of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Environmental Tobacco Smoke Hazards and Benefits of Work-Site Nonsmoking Programs

CONSIDERABLE EVIDENCE EXISTS that exposure to environmental tobacco smoke (ETS) is harmful to the health of nonsmokers. The United States Environmental Protection Agency (EPA) recently classified ETS as a class A carcinogen, meaning that it has been shown to cause cancer in humans.

Environmental tobacco smoke consists primarily of cigarette smoke that is generated while a cigarette is smoldering, plus a smaller amount of mainstream smoke that smokers exhale. From a burning cigarette, 75% or more of the combustion products enter the air. The constituents of ETS are qualitatively similar to those of mainstream smoke, but many constituents—particularly ammonia, formaldehyde, and nitrosamines—are present in much higher relative concentrations in ETS than in mainstream smoke.

On average, nonsmokers with exposure to ETS absorb a dose of nicotine equivalent to actively smoking a sixth to a third of a cigarette per day. Although this may seem like a small amount, such an exposure can be substantial over time. For example, it is estimated that a nonsmoking flight attendant who works international flights where smoking is allowed absorbs the equivalent of 1,000 to 2,000 cigarettes over the course of a career. Some people, particularly small children in poorly ventilated homes and workers in bars or restaurants, may have higher than average levels of exposure. Exposures to ETS at home and at work appear to be additive.

The means of reducing smoking's adverse occupational effects are increasingly well established. When work-sites are smoke-free, workers have lower levels of heavy or continuing smoking and higher levels of smoking cessation. Many (37%) large California corporations subsidize smoking cessation services (beyond health insurance). The wisdom of these services is becoming accepted, with the demonstration that even a modest participation in work-site smoking cessation programs (or employee time without nicotine patches) reduced absenteeism. Nicotine patches have developed an excellent safety record, and patch supply problems have been overcome.

Respiratory tract illness is more common in children who have exposure to environmental tobacco smoke. Infants with exposure to ETS have an increased risk of hospital admission for respiratory tract infection in the first year of life, with a greater risk directly linked to the number of cigarettes that the infant's mother smokes. The EPA estimates that 150,000 to 300,000 cases of lower respiratory tract infections in infants and children before 18 years of age occur that are attributable to ETS.

Other childhood health hazards include an increasing prevalence of wheezing and middle ear effusions, the latter possibly related to upper airway infection or the aggravation of atopic illness. Airway hyperresponsiveness, as determined by responses to inhaled methacholine, has recently been shown to be more common in children of parents who smoke than in children whose parents do not smoke. The EPA has estimated that 200,000 to 1,000,000 children with asthma have their condition worsened by exposure to ETS. Estimated by increases in the forced expiratory volume with increasing age, growth in lung function is reduced in children whose parents smoke (although the clinical relevance of this finding is unclear). Sudden infant death has been shown in several studies to be more likely to occur in children of persons who smoke.

More than 30 epidemiologic studies have examined the risk of lung cancer in nonsmokers whose spouses smoke. Most of these studies report an increased risk of lung cancer associated with exposure to ETS, including several studies showing a risk that is proportional to the

number of cigarettes that the spouse smoked. After various corrections for confounders, the overall relative risk for lung cancer from ETS in nonsmokers is estimated to be about 1.2, accounting for an estimated 3,000 lung cancer deaths annually in the United States in nonsmokers.

Several epidemiologic studies have found an association between ETS exposure and an increased risk of myocardial infarction in nonsmokers with spouses who smoke. On average, ETS exposure has been associated with a 30% increased risk of coronary heart disease, which has been estimated to cause as many as 37,000 premature deaths in the United States annually.

Several studies have reported substantial reductions in pulmonary function in adult nonsmokers with exposure to ETS at home, at work, or both. The clinical import of these findings is uncertain. Although research is conflicting, asthma in adults has been reported to be aggravated by ETS. When exposed to ETS, nonsmokers often complain of eye irritation, nasal congestion, headaches, and coughing. Although these symptoms are prevalent in nonsmokers with exposure to ETS, they are more severe in people who have a history of allergies.

An appreciation of the hazards of environmental tobacco smoke is important to practicing physicians for several reasons. It provides a basis for advising parents not to smoke when there are children in the home. It provides a basis for insisting that child-care facilities be smoke-free. It provides a basis for recommending smoking restrictions in work sites and other public places. These restrictions at home or at work sites often result in smokers quitting smoking.

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Chemical Inhalation Injury and Its Sequelae

FEW EVENTS CONCERN the public as extensively as a mass outbreak of a toxic chemical illness. The recent release of sulfuric acid into the environment in Richmond, California, sent more than 20,000 persons seeking acute medical care. Despite the relatively self-limited nature of most of the symptoms reported, this "hazardous material incident" overwhelmed the local health care system and is sure to result in a lengthy legal liability process. This was only the most dramatic in a series of releases that seem to cloud the environmental health horizon, such as the methyl isocyanate tragedy in Bhopal, India. The metam sodium contamination after a train derailment in Dunsmuir, California, reminded us that large-scale exposures to relatively exotic chemicals, about which little reliable toxicologic data are available, can occur close to home.

Irritant-inhalation injury is relatively common and can occur in a variety of circumstances. For example, poison control centers nationwide receive about 60,000 chemical inhalation case referrals annually, of which a third to a half are due to irritants. The most common single chemical cause of irritant illness appears to be chlorine. Chlorine exposure scenarios include transportation release, occupational exposure, the misuse of household cleaning products, and pool chemical mishaps. This variety of circumstances underscores the strong link between occupational and environmental medicine in preventing and treating chemical inhalation injuries.

In recent years, growing attention has been given to the possible long-term sequelae of irritant-inhalation injury. Typically an intense, high-level exposure causes clear-cut respiratory symptoms, such as cough, wheeze, or dyspnea, beginning immediately or shortly after the irritant is inhaled. The symptoms usually lead to medical evaluation immediately, frequently with an empiric prescription of an inhaled bronchodilator. In general, these exposures rarely result in even a brief hospital admission; most cases resolve over hours to days. Nonetheless, a subset of patients (it appears to be less than 10%) continues to complain of persistent respiratory symptoms and to show increased nonspecific airway responsiveness on challenge testing. This phenomenon has been given different names, including "reactive airways dysfunction syndrome" and, alternatively, "irritant-induced asthma." The latter term may be preferable for more general use because it includes cases where the irritant exposure is subacute or long-term, rather than being limited to short-term exposures alone.

Research is limited on the mediating factors that may predict who will go on to have persistent symptoms and increased airway responsiveness after irritant exposure. Cigarette smoking may play a role. Our understanding of ongoing symptoms is further complicated by the psychic distress that often follows mass inhalation exposures, with some patients meeting the diagnostic criteria of post-traumatic stress syndrome.

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Rehabilitation of Occupational Low-Back Pain—Avoiding Unnecessary Disability

LOW-BACK PAIN is the most common cause of disability in workers younger than 45 years and the second most common cause in those 45 to 65 years old. It is also the most expensive occupational injury, with the 10% of pa-

tients off work the longest accounting for 80% of all costs. Few treatments with proven effectiveness exist for lower back pain. Passive modalities based on rest and pain relief—medications, bed rest, and soft-tissue treatments—may discourage recovery and, if used for extended periods, prolong time lost from work. As with any injury, if lost time exceeds six months, the possibility of the patient returning to work becomes remote. Complicating occupational back injuries are a disability-oriented compensation system and many emotional factors—job dissatisfaction, feelings of entitlement for compensation, life distress, depression, and dysfunctional behaviors such as addiction. To avoid unnecessary disability, physicians should treat patients with occupational low-back pain with an active program of physical reconditioning and education. In addition, emotional factors that interfere with a return to work must be uncovered and addressed in the treatment plan.

Programs for athletes, whose goal is a rapid return to sports participation, encourage mobility, flexibility, and strength. Strength and range of motion determine when an athlete may return to competition, and the same principles are applied to patients with occupational low-back injuries. Injured workers treated like injured athletes, with emphasis on recovering function rather than only eliminating pain, have a greater sense of involvement in their care, improved motivation, greater relief of symptoms, and better rates of returning to work. Workers informed about their diagnoses, involved in a physical reconditioning program, and taught techniques for preventing reinjury and pain control are more satisfied and more apt to comply with rehabilitation. A 1991 study summarized the success of aggressive physical rehabilitation programs in relieving pain, returning injured workers to work, and preventing low-back injuries.

The history and physical examination can help identify the minority of patients with urgent neurologic compromise, malignancy, infection, or systemic disease who may require electrodiagnostic or imaging studies and referral for surgical evaluation. Most patients with occupational lower back pain will not need radiologic studies or surgical evaluation, but will need initial pain relief to control symptoms and promote activity. Excellent results have been achieved with a short course of opioid or nonsteroidal anti-inflammatory medications and with two days or less of bed rest. A program of conditioning and endurance exercise—walking, biking, swimming—begins after the first office visit. A simple regimen is devised to allow the patient to increase function progressively. Individual exercise programs are tailored to each patient by a physician or physical therapist or taught to groups of patients in a "back school" format.

Communication among the physician, patient, employer, therapist, and insurer allows for individual case management and a return-to-work plan. Patients and supervisors are encouraged to design acceptable modified duty. The benefits of social support, accomplishment, and income maintenance that accrue when a patient returns to the work site in a modified capacity assist in the return to full duty. Discussing the workers' compensation system with patients helps them to set realistic expectations regarding compensation and the process of retraining. Energy spent by patients on symptom embellishment can be channeled into more productive explorations of career options and life changes.

Factors that might interfere with recovery, such as job dissatisfaction and life distress, also need to be considered. Evaluation by a counselor or psychologist can uncover issues of illiteracy, depression, addiction, or dysfunctional behavior. Recommendations are then made for dealing with the emotional issues along with the physical symptoms. Workers may need psychotherapy, remedial education, marital counseling, or treatment of alcohol and drug-related issues. A supportive, nonadversarial attitude from the primary care physician is essential. Education and emotional support may help an otherwise poorly motivated patient to begin functional recovery.

Back pain from work-related injuries need not result in back pain disability. Treatment based on a sports medicine model of progressive function is effective in returning injured workers to their preinjury condition. Medical treatment alone, however, is often insufficient. Evaluating patients' difficulties at work and at home may provide the key to therapeutic success. Physical reconditioning, plus patient education, communication with the workplace, and emotional support for workers all contribute to improved results and decreased disability.

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Separating Noise-Induced From Age-Related Hearing Loss

AFTER A LONG CAREER of excessive noise exposure, workers will have hearing loss from at least two causes: occupational noise and aging. Epidemiologic studies have usually assumed that decibel losses were additive, calculating a noise-induced permanent threshold shift by subtracting control-group thresholds (aging alone) from exposed-group thresholds (aging plus noise). Studies involving subjects with exposure to noise early or late in their careers have tended to support the theory that noise-induced and age-related losses are additive.

The International Organization for Standardization has recently published a standard, ISO-1999, that summarizes the epidemiologic data relating hearing loss to aging and noise. For a specified sex and audiometric frequency, this standard models an age-related permanent threshold shift as an accelerating (quadratic) function of age. Given frequency and noise exposure level, the noise-induced

shift is represented by a decelerating (logarithmic) function of duration. Selected percentiles (10th, 50th, 90th) at ten-year intervals are tabled, but formulas are provided for calculating other distribution and time points.

The ISO-1999 document provides a method for predicting the distribution of hearing levels in a population of noise-exposed workers of known age, sex, exposure level, and exposure duration: the age-related permanent threshold shift and noise-induced shift are added, with a variable adjustment (when age-related and noise-induced shifts are both large, the expected overall hearing level is less than their simple sum). Speech-frequency noise-induced shift is strongly related to exposure level: after 40 years at 85 dB on the A scale (dBA), the median expected noise-induced shift is only about 2 dB compared with a 20-dB noise-induced shift for 40 years at 100 dBA. For example, for 65-year-old men, the median expected age-related shift (about 14 dB) exceeds the 40-year median expected noise-induced shift for exposure levels below 97 dBA.

These models can also be used for a retrospective analysis of hearing loss claims. If exposure levels are known or can be estimated and if a diagnosis of hearing loss due to aging and noise is clinically justified, the most likely relative contributions of aging and noise are easily calculated, even if only a single recent audiogram is available. A valid series of audiograms that spans a worker's career documents the growth of hearing loss over time. An accelerating curve suggests a predominance of aging changes, while a decelerating curve suggests noise was the more important factor. Methods of allocation (or apportionment) are also available to deal with workers with asymmetric or unusual audiograms, as well as changing exposure levels and multiple causes of hearing loss. Although considerable professional judgment may be required to select the appropriate methods of analysis, ISO-1999 provides an internationally useful framework for both prospective and retrospective analyses of occupational hearing loss, especially for separating noise-induced from age-related changes.

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Evaluating and Preventing Illness Associated With Indoor Air Pollution

HEALTH EFFECTS ASSOCIATED with exposure to indoor air pollutants are diverse, ranging from acute irritation of the eyes and upper respiratory tract and bronchoconstriction to chronic inflammation, fibrosis, and cancer. A physician's challenge is to recognize the possible connection between many nonspecific symptoms and exposures to one or more pollutants and to provide appropriate management.

Although lung cancer from exposure to asbestos and radon is of great public health concern, the clinical relevance of these exposures is small compared with the morbidity associated with other indoor air pollutants. The major sources and types of indoor air pollution include combustion emissions, noncombustion emissions, and biologic agents.

Sources of combustion emissions include tobacco smoking, cooking and heating with gas-fueled appliances, and wood burning. The principal emissions of combustion, carbon monoxide, nitrogen dioxide, and particles, are associated with adverse health effects. The health effects of carbon monoxide have been extensively described and range from impaired exercise capacity among patients with heart and lung disease at low levels of carboxyhemoglobin (2% to 6%) to coma and death (above 40% carboxyhemoglobin). Nitrogen dioxide at concentrations found in US homes has been implicated as a cause of an increased incidence of lower respiratory tract infections and decreased lung growth in children. Particles have been associated with irritation and inflammation of the eyes and respiratory tract. Noncombustion emissions include formaldehyde and other volatile organic compounds from carpet, particle board, cleaning products, solvents, paints, and pesticides. Exposure to these compounds may cause eye and upper respiratory tract irritation and may also result in systemic symptoms, including headache, dizziness, fatigue, and malaise.

Numerous sources of biologic aerosols such as spores, bacteria, and organic particles from insects and animals may be present in indoor settings, particularly in the home. Moisture from the use of humidifiers and water damage may create conditions conducive to mold and fungi growth, and animals kept indoors may lead to the accumulation of dander. Exposure to these biologic agents may lead to upper and lower respiratory tract infection, hypersensitivity pneumonitis, and the development and exacerbation of asthma.

The term "building-related illness" refers to specific disorders caused by any of the agents previously described. In contrast, the "sick-building syndrome" pertains to a high prevalence of nonspecific symptoms among building occupants in the absence of an identifiable source or elevated levels of pollutants. Features of the sick-building syndrome include lethargy, headache, difficulty concentrating, and irritation of the eyes, nose, and throat. While the cause of a building-related illness must be determined before a solution can be implemented, establishing the exact cause of sick-building syndrome is usually not possible. Interventions for this syndrome are often complex and include removing and controlling possible sources, increasing building ventilation, and cleaning ventilation systems.

A carefully obtained history that includes an assessment of home and work environments and questions to assess the relationship of symptoms to time spent in home

and work settings may provide the link between a patient's problems and indoor pollutants. Removing the pollutant source is the preferred method to reduce exposure and prevent symptoms and disease. Although other strategies to limit exposure, such as increased ventilation and the use of air cleaners, are available, they may have limited effectiveness and may be costly. Adjusting medication regimens and using masks (respirators) have not been adequately investigated and cannot be recommended at present.

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Bioaerosols

SINCE THE RECOGNITION of pneumonia among Legionnaires attending a convention in 1976, there has been increasing interest in diseases associated with indoor exposure to microbial agents, commonly referred to as bioaerosols.

Bioaerosols are airborne particles, large molecules, or volatile compounds that are living or released from a living organism. Airborne bacteria, fungi, and viruses are well-recognized bioaerosols, but arthropods, birds, and mammals also produce effluents—such as mite feces, skin scales, and cat saliva—that constitute bioaerosols as well.

Three conditions are required to produce bioaerosols: a reservoir (either environmental or human), amplification, and dissemination (aerosolization). For example, *Legionella pneumophila* organisms reside in soil, water, and streams; can amplify in cooling towers, whirlpools, shower heads, and humidifiers; and may disseminate in aerosols or effluents to cause pneumonia.

Infections and hypersensitivity illnesses are the major diseases associated with bioaerosol exposures in buildings. The *L pneumophila* bacterium is associated with both a lethal pneumonia and with Pontiac fever, an influenzalike illness with a high attack rate (90% to 100%) and short incubation period (36 hours). Viral pathogens are disseminated from human reservoirs, and the risk for adenovirus infection may be increased in "tight" buildings. Unusual infectious organisms, such as rickettsiae, can disseminate in specialized environments such as hospitals and laboratories.

The spectrum of hypersensitivity diseases associated with bioaerosol exposures includes rhinitis, asthma, and hypersensitivity pneumonitis. Bioaerosols containing fungal organisms (such as *Alternaria* and *Aspergillus* species), arthropod contaminants in house dust, plant pollens, and mammalian danders and proteins can cause allergic rhinitis and asthma. Eosinophilia, elevated immunoglobulin E antibody levels, and immediate skin-prick-test reactivity to the specific aeroallergens are often found in bioaerosol-induced cases of asthma and rhinitis. Hypersensitivity pneumonitis resulting from exposure to bioaerosol-contaminated buildings is typically manifested by nonspecific symptoms, such as cough, chest tightness, dyspnea, malaise, and fever. Recognition requires a high index of clinical suspicion and, often, early bronchoscopy to detect lymphocytic alveolitis and granulomatous interstitial lung disease.

Quantitative bioaerosol sampling may be indicated where building-related outbreaks of infection or hypersensitivity disease are identified. Sampling should be done by an industrial hygienist who is aware of machine calibration, sampling time, and the need for appropriate (typically outdoor) controls. Specimens should be analyzed by laboratories experienced in environmental microbiology. Bioaerosol sampling interpretation is limited by a lack of information on dose-response relations, inadequate knowledge of acceptable bioaerosol levels, and variability in measurement methods. Negative results do not assure that no problem exists.

An unusual exposure is considered one in which the bioaerosol concentrations are at least an order of magnitude higher than those in the control environment, or one in which the types of organisms or other bioaerosols in the occupied space are different from those in the control environment. The finding of elevated levels or an unusual organism in an indoor environment, however, does not necessarily prove a causal relation between the exposure and symptoms.

The control of bioaerosol exposures in indoor environments may involve preventing the entry of outdoor contaminants (such as keeping windows and doors closed), preventing amplification on indoor substrates (such as cleaning or eliminating standing water reservoirs that support microbial growth such as humidifiers, dehumidifiers, drip pans, and standing water in plant trays), and removing contaminant sources (such as water-damaged carpets, furniture, or ventilation duct filters). Preventive maintenance to avoid conditions that promote microbial growth is probably the most important method for controlling bioaerosols in buildings.

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Tuberculosis and the Need for Respiratory Protection for Health Care Workers

WORKERS WITH EXPOSURE to airborne toxins must use respirators or other forms of respiratory protection required by the Occupational Safety and Health Administration (OSHA). The recent increase in the incidence of drug-

resistant tuberculosis, partly associated with the spread of the human immunodeficiency virus, has led to concern that health care workers in high-risk settings are not adequately protected from work-related exposure to tuberculosis.

Since 1988, several hundred health care workers are estimated to have acquired tuberculosis from workplace exposure. Of particular concern is that at least 16 health care workers have been infected with drug-resistant tuberculosis in outbreaks at seven hospitals and one prison. Control measures to reduce the risk of work-acquired tuberculosis include patient isolation, negative-pressure rooms, medical surveillance of health care workers with possible exposure, and a respiratory protection program. Without such measures, the extensive spread of tuberculosis, including the drug-resistant form, among health care workers is a real possibility.

A number of studies have shown that surgical masks are ineffective as a precaution against airborne infection. These masks are designed to protect patients, not health care workers. Surgical masks cannot effectively filter the 1- to 5-μm droplet nuclei that form when larger tuberculosis-containing droplets evaporate, nor can they provide an effective face seal. Only properly fitted respirators with high-efficiency filters comply with guidelines from the National Institute of Occupational Safety and Health, OSHA, and the Centers for Disease Control and Prevention (CDC) for protection from tuberculosis. Placing surgical masks on patients is recommended only as a temporary measure when patients are outside isolation rooms. Although the volume of exhaled aerosols is reduced somewhat when patients wear masks, outward leakage will still occur.

The Occupational Safety and Health Administration announced that in 1994 it would issue citations to employers who lacked a tuberculosis control program for health care workers with exposure to patients with suspected or confirmed tuberculosis or who performed or assisted with a "high hazard procedure," including nebulizer treatments, bronchoscopy, sputum induction, suctioning, and autopsies.

Draft guidelines issued by the CDC in October 1993 called for the use of respirators that would provide filtration of at least 95% of particles 1 μm in size (about the size of a droplet containing bacteria) and that could be fitted to obtain a face seal of no more than 10% leakage. In other words, respirators would have to have a protection factor of 10 or greater. This exceeds the protection available from dust mask-type respirators. The Occupational Safety and Health Administration currently requires high-efficiency particulate aerosol (HEPA) filtered respirators for protection against tuberculosis. Most HEPA respirators are twin-cartridge clastomeric face-piece industrial models, although a few disposable HEPA respirators are now available. A powered air-purifying respirator may be used to provide protection without the need for fit testing or when a health care worker has facial hair that would interfere with seal.

Engineering controls are the preferred means of hazard control. Negative-pressure isolation rooms and treatment booths, HEPA-filtered ventilation systems, and, possibly, germicidal irradiation are appropriate engineering safeguards for tuberculosis control. Administrative controls, such as reducing the number of persons who enter isolation rooms, may be useful in reducing the number of possibly exposed workers who require respiratory protection. The Occupational Safety and Health Administration also recommends medical surveillance of hospital employees by means of tuberculosis skin testing on employment and at least annually thereafter. Health care employers also must become familiar with the administration and technology of respiratory protection. Written respiratory protection programs, fit testing, respirator selection protocols, medical determinations, and training are required whenever respirators are used. Opposition from the hospital community and health care workers themselves must be overcome. A 1992 attempt by the New York OSHA regional office to require a respiratory protection program in hospitals met with deep-seated resistance and a barrage of complaints. How successful hospitals will be in implementing respiratory protection programs for large numbers of workers remains to be seen.

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Hepatitis B Immunization

About 300,000 persons in the United States become infected with the hepatitis B virus (HBV), and about 3,000 persons die each year of fulminant hepatitis, cirrhosis, and hepatocellular carcinoma related to HBV infection.

Plasma-derived hepatitis B vaccine (Heptavax-B) has been licensed in the United States since 1981 and recombinant vaccines (Engerix B, Recombivax HB) since 1986. Hepatitis B vaccines are standardized for potency, and thimerosal is used as a preservative. Both plasma vaccine (which is sterilized in three steps, all of which inactivate the human immunodeficiency virus and all classes of viruses) and recombinant vaccines are safe and immunogenic (greater than 90% protective antibody response). Plasma-derived vaccine is indicated only for hemodialysis patients and other immunocompromised hosts and persons with yeast allergy. The recommended series in three doses is administered intramuscularly in the deltoid muscle (adults and children) or anterolateral thigh (infants and neonates) at zero, one, and six months. Poor immune responses to the vaccine in adults have been documented when administered in the buttock.

Postvaccination testing and revaccination are not rou-

tinely recommended, but a knowledge of the antibody status may be helpful for health care workers at risk for injuries from sharp instruments. Postvaccination testing should be done between one and six months after finishing the series. Despite observed drops in antibody levels over time, data to date suggest vaccinees remain protected against hepatitis B disease. Whether revaccination is necessary after an extended period awaits further longitudinal data. The need for booster doses in health care workers after exposure and in hemodialysis patients should be based on antibody testing.

Universal infant immunization with hepatitis B vaccine was recommended in 1991 by the Immunization Practices Advisory Committee of the US Public Health Service and in 1992 by the American Academy of Pediatrics and American Academy of Family Physicians. Universal infant immunization is a component of an overall strategy by the US Public Health Service to eliminate hepatitis B transmission, which includes screening all pregnant women and vaccinating adolescents and adults in high-risk groups.

Universal infant immunization has been shown to be cost-effective and cheaper than well-accepted interventions such as smoking cessation and pneumococcal vaccine. Although the risk for hepatitis B for children in uninfected households does not rise until adolescence, routine childhood immunization offers the advantage of an established vaccination delivery system and somewhat cheaper vaccine costs. Targeting high-risk adults for hepatitis B vaccination remains a priority, although about a third of adults with acute hepatitis B have no identified risk factor.

Seroprevalence studies indicate that health care workers, depending on the frequency of blood contact, are 6 to 60 times more likely to be infected with HBV than persons in the general population. The Occupational Safety and Health Administration issued new regulations in 1992 requiring that free hepatitis B immunization be offered to health care workers with possible contact with blood or blood-contaminated body fluids. Each facility should designate a responsible person to ensure that information and training on the prevention of bloodborne pathogens in the workplace, including the indications for hepatitis B vaccine, are provided annually with appropriate documentation to workers at risk.

Other groups at high risk for HBV infection include clients and staff of institutions for the developmentally disabled, hemodialysis patients, sexually active homosexual men, users of illicit injectable drugs, persons receiving clotting factor concentrates, household and sexual contacts of HBV carriers, long-term inmates of correctional facilities, and sexually active heterosexual persons.

Hepatitis B infection is endemic among Alaska Natives, Pacific Islanders, and in many countries of Asia and Africa. Long-term international travelers to these areas are also candidates for hepatitis B vaccination.

For prophylaxis after exposure—such as in infants born to women with the hepatitis B surface antigen (HBsAg) and persons with needle-stick exposure to HBsAg-positive blood—the administration of both hepatitis B immune globulin and vaccine is indicated. Package inserts should be consulted for variations in dosage and immunization schedules for different licensed products for prophylaxis before and after exposure.

The number of cases of hepatitis B has declined in the United States since 1985, but the incidence rate of acute hepatitis B is only now dropping below the rates of the late 1970s. Sustained efforts at a wider application of hepatitis B vaccine are needed.

Simplifying the immunization schedule and an oral vaccine using recombinant technology would be welcome advances.

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Alerts, Notices, and Case Reports

The Forgotten Ureteral Stent

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URETERAL STENT placement is an important adjunct to many urologic procedures such as extracorporeal shock wave lithotripsy and ureteroscopy.[1] Ureteral stents may also be useful for managing conditions such as hydronephrosis during pregnancy, ureteral trauma or strictures, and obstruction due to a malignant neoplasm or retroperitoneal fibrosis. Indwelling stents should be changed at regular intervals—for instance, every six to eight weeks—or be removed because of the well-known risks of stent incrustation and obstruction.[2,3] One author advised keeping a log of patients with indwelling stents to ensure timely stent changes and removal, thus avoiding having patients "fall through the cracks."[4] We report the case of a patient with a retained stent for 18 years following an open urologic procedure.

(Fishman JR, Presto AJ III: The forgotten ureteral stent. West J Med 1994; 160:569-570)

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Report of a Case

The patient, a 65-year-old man, underwent a left ureterolithotomy in 1975 with placement of a straight Silastic (silicone) ureteral stent secured with a 4-0 chromic suture. The patient kept only one appointment after the operation but recalled no instrumentation to remove the stent. Unaware of the stent's presence, the patient experienced occasional loin pain in subsequent years but did not seek medical attention. The recent onset of urinary frequency prompted a urologic evaluation. An intravenous pyelogram showed two pelvic calcifications on the scout film (Figure 1, left), with substantial left hydroureteronephrosis from an obstructing distal ureteral calculus (Figure 1, right). Endoscopy showed the stent with one end embedded in a large bladder stone and its other end impaled in the bladder wall. After we briefly at-

Figure 1.—Left, An intravenous pyelogram scout film shows 2 large pelvic calcifications. **Right,** the 20-minute film shows a large bladder stone and left distal ureteral calculus causing hydroureteronephrosis.

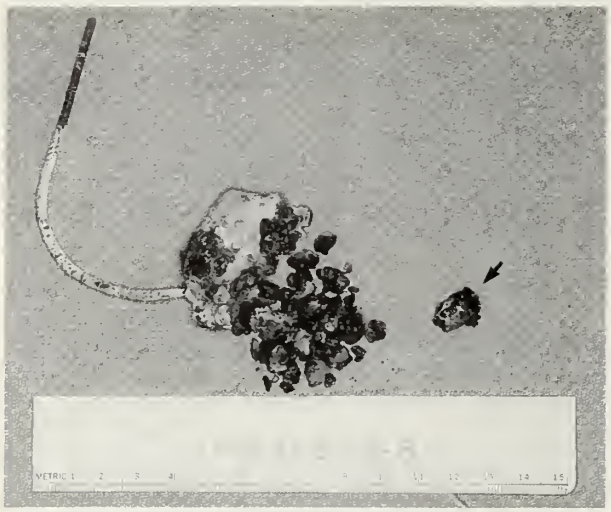

Figure 2.—The bladder stone is shown partially comminuted, with an embedded stent and a ureteral calculus (**arrow**).

tempted electrohydraulic lithotripsy to comminute the bladder stone, we did a cystolithotomy and ureterolithotomy to remove the calculi and stent (Figure 2). Inspection of the ureteral calculus revealed a piece of the stent passing through the core.

Discussion

Ureteral stents were popularized in the late 1960s with the availability of silicone tubing that could be passed endoscopically.[5] Over subsequent years, stents were modified in composition[6] and configuration.[7] The straight silicone ureteral stent placed in our patient was prone to migration, accounting for most of it passing into his urinary bladder.

Bladder stones in men usually result from factors promoting urinary stasis, including prostatic hypertrophy, bladder diverticulum, or urethral stricture. Cytoscopy enabled us to determine that our patient had a retained ureteral stent which served as a nidus for stone formation. Previously a patient was reported to have a heavily calcified ureteral stent retained for two years.[3] Several authors have discussed the need for ancillary procedures to remove calcified ureteral stents.[3,8] Another patient was reported to have a retained ureteral stent for 17 months that fractured, requiring several methods to retrieve.[9] To our knowledge, 18 years is the longest reported duration for a retained ureteral stent.

Patients with indwelling ureteral stents may report a variety of symptoms, including loin pain, lower abdominal pain, hematuria, dysuria, frequency, and nocturia.[10] These symptoms are presumably caused by irritation from the presence of the foreign body. Alternatively, it has been suggested that a ureteral stent causes little or no discomfort, and most patients tend to forget its presence.[4] Our case report supports this idea, given our patient's sustained tolerance for the forgotten stent and stone burden. Stent removal will generally alleviate most troublesome symptoms, although nocturia may be a persistent complaint for reasons that remain unclear.[10]

While the urologist placing a ureteral stent will ultimately be responsible for its management, patients may seek assistance from their primary physicians for symptoms referable to the stent that can be addressed based on an understanding of the reasons for stent placement and the duration of the stent's presence. Most important, this report reemphasizes the need from a medical and legal standpoint to ensure patient compliance with appropriate follow-up once stents are placed.

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Necrotic Arachnidism

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SPIDER BITES are common; most produce minor local irritation requiring no treatment. There is a group of spiders, however, known to produce cutaneous necrosis and various systemic symptoms. *Loxosceles reclusa* (the brown recluse spider) may be blamed for all necrotic spider bites, even in parts of the country where it is not found. We present two cases incriminating another spider, *Tegenaria agrestis*, as the causative agent. Recognizing the bite of *T agrestis* may be important to anticipate possible serious late complications.[1-3] In addition, the inappropriate inclusion of victims of *T agrestis* bites in studies of new therapies for *L reclusa* spider bites may invalidate those studies.

(Fisher RG, Kelly P, Krober MS, Weir MR, Jones R: Necrotic arachnidism. West J Med 1994; 160:570-572)

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Figure 1.—A bite wound of *Tegenaria agrestis* is shown on a 2-year-old boy's leg 3 days after it is first seen.

Report of Cases

Patient 1

A lesion developed on the back of the leg of this 24-month-old male toddler. The patient's father, a physician, described it as an 8-mm firm papule with a central pustular area that was not tender. There had been no crying or change in the child's behavior at any time during the day to suggest that the bite had been painful. Erythema and induration increased over the next 24 hours. Three days later the center of the lesion was punctate, with a discolored, necrotic center covered with an eschar (Figure 1). Other than an oral antibiotic, no treatment was given, and the lesion resolved in about four weeks. No systemic manifestations developed. There is a residual scar. A search inside and outside the patient's home readily recovered several specimens identified as *T agrestis* (Figure 2).

Patient 2

The patient, a 17-year-old girl, walked into a spider web. She felt no pain at the time, but saw a large brown spider in the area. Later that evening she noted the appearance of lesions she described as "pimples" on her right proximal dorsal forearm and right palm. The lesions progressed to develop necrotic centers. She was seen two days later with a 1-cm area of necrosis surrounded by a 4-cm area of erythema on the right forearm and a smaller 3-mm area of necrosis on the right palm. She had no systemic illness. The larger lesion was unroofed and debrided. Both lesions healed well with no residual scarring.

Discussion

In the usual clinical setting, the spider actually responsible for a clinically notable bite is seldom recovered and identified. Circumstantial evidence is used to presume the identity of the offending spider. Although reports have attributed necrotic lesions to the bites of *Loxosceles, Chiracanthium, Argiope, Lycosa,* and *Phidippas* species, nearly all bites in this country have been thought to be caused by *Loxosceles reclusa.*[4] The importance of *Tegenaria agrestis,* although mentioned in toxinology journals, has not been widely recognized. In fact, two recent reviews of spider bites fail to mention this species.[5,6] Consequently, clinicians are prone to blame all necrotic spider bites on the recluse.

We report the cases of two patients in Tacoma, Washington, with necrotic spider bites that incriminate *T agrestis* as the responsible agent. A search of the patients' homes revealed several *T agrestis* and no other specimens known to produce necrotic lesions. It is important to remember that the brown recluse spider is not found in the Northwest.[4] Additional support for *T agrestis* as the causative agent comes from the work of Vest, who has reported numerous additional cases of probable *T agrestis* envenomation,[3] in some cases with recovery of the spider responsible for the bite. Necrotic skin lesions have been reproduced in animals as well.[7]

Tegenaria agrestis has been variously referred to in the literature as the aggressive house spider (it is not aggressive, despite claims to the contrary[8]), the hobo spider, the Walckenaer spider, the northwestern brown spider, and the funnel-web spider. The last name has been used because of the spider's distinctive funnel-shaped web; it should be remembered, however, that the spider most often called the funnel-web is an Australian spider (*Atrax robustus*) that is deadly and is not related to *T agrestis.* Because reports in this country have thus far been limited to the Northwest, we prefer the name "northwestern brown spider."

Our two patients had necrotic skin lesions but no systemic symptoms. Their clinical course was consistent with that of previously reported cases as follows[9]:

- First, a small reddened area of induration appears, often with surrounding erythema;
- A vesicle or vesicles appear 15 to 35 hours later;
- About 24 hours later, the vesicles burst, and serum oozes;
- Eschars form for lesions left dry;
- Subeschar necrosis then develops, which can be limited or extensive.

Both local and systemic reactions to the northwestern brown spider bite may be less severe than those to the brown recluse. Thus, response to therapy may be different.

About 40% of patients with *Tegenaria* bites appear to

Figure 2.—A male *Tegenaria agrestis* spider was recovered from the home of patient 1. The average body length of *T agrestis* spiders is 10 mm (range, 7 to 14 mm), with a leg span of 35 mm (range, 27 to 45 mm).

have some systemic symptoms.[2,9] The most prominent of these is headache, which begins anywhere from 30 minutes to several days after the bite (usually within 10 hours). Headaches are severe, last two to seven days, and are only minimally responsive to analgesics. There may be associated visual symptoms not unlike those of migraine. Auditory and visual hallucinations also occur, and many other patients report "feeling odd," as though they had taken a psychotropic drug. One patient reported that the feeling mimicked the effects of psilocybin.[9]

Weakness and lethargy are also common and can be severe and protracted. In a recent series, four of nine victims of *T agrestis* bites had such profound weakness that they were unable to walk unassisted for as long as seven days after the bite.[3]

Other systemic effects include dry mouth, anorexia, dizziness, disorientation, joint pain, paresthesias, and mild dyspnea.

About 15% of *T agrestis* bite victims have hemodynamic changes, notably a reduction in platelet number, erythrocyte spherocytosis, and hemolysis. Another 5% of patients have severe systemic responses that may include intractable vomiting or secretory diarrhea. Rarely, a delayed aplastic response has been associated with the bite of *T agrestis*, with pancytopenia beginning about three weeks after the bite.[2] The cause of this reaction is not known. One case of severe, refractory aplasia culminated in death.[3] The bite of *T agrestis* appears to be the only bite or sting that has been associated with pancytopenia.

Our patients were bitten in the summer months, a season usually associated with bites by the mature male. The bite of the mature male is most common and produces cutaneous necrosis often accompanied by the systemic manifestations outlined earlier. The bite of the mature female is seen more commonly in October or November. It produces a well-defined cutaneous erythematous macule that develops a pinpoint white vesicle in its center, then is reabsorbed. It does not usually produce notable subcutaneous necrosis and may not induce systemic manifestations. Laboratory experiments have shown that the venom of the male spider contains substantial quantities of two proteins that are found in only trace amounts in the venom of the female.[2]

The bite of immature *T agrestis* spiders may produce envenomation equivalent to, or more serious than, that seen in the bites of adult spiders. Bites seen during the winter months, when adult spiders are absent, are uncommon; however, they are frequently accompanied by severe local and systemic reactions.[3]

Our patients appeared to have no pain at the time of the bite. This lack of pain may be helpful in recognizing these bites. *Tegenaria agrestis* appears to be the most common cause of serious spider bites in the Pacific Northwest. Physicians, particularly those in the Northwest, need to be aware of the possibility of bites by the northwestern brown spider.

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Commentary

Medicine and the Minotaur

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Medicine's direction? We do not know. We do not know the end of medicine's trail. We do not even know the beginnings of our profession, back in dim history. We barely know why we chose our own personal paths in this magnificent field. We do know that from time immemorial, healers have healed because patients trust and believe in them. Now we feel that trust and belief waning. In her address to the graduates of the University of California, Davis, School of Medicine, Faith Fitzgerald examined our roots and their cankers, our values and their distortions. Most of all, she reminded graduates then as she reminds us now about the privileges of being a physician.

LINDA HAWES CLEVER, MD
Editor

Ceremonial investitures, such as graduation from medical school, divest men and women of their private characters and clothe them in the mantle of their vocation. Whatever else you may do or be after today, you will be doctors of medicine—and that identity is special. But it is not given you by this ceremony; neither by your teachers, nor the university, nor even by your own efforts—though all have played a part. Your identity as physicians is given you by one thing only—the fact that there are patients who will submit themselves to your care. The only reason any of us can practice our art is because patients allow us to. They give us this right because they believe in our goodness and our skill. So it is not the physician, nor the system, nor the science, nor even the education that is at the core of your physicianhood—it is the trust that patients give you.

Consider for a moment how remarkable this trust is: patients tell us the most secret facts about themselves (hidden even from their families), they let us render them unconscious, paralyze them, cut off parts of their bodies, give them potential poisons, manipulate their lives and even the lives of their children—it is breathtaking! And they allow us to do this because they believe that the principal desire of their physician is to help them. And they know that because we give them our word that this is so.

In fact, the really distinctive event that occurs at graduation from medical school, the thing that makes you after today different from what you were when the day began, is the physician's oath—that promise, almost unique in secular life, that you make to these patients. There are many permutations of the oath, but all—*all*—distill to this: once you take the oath, you are bound to the service of the sick as the central meaning of your life. It is upon this promise that your patients rely for their lives and for which they give you respect and status as well as trust.

So graduation marks the beginning of a partnership—trusting patient and serving physician. It works well if physicians and patients continue to believe in one another. But something has seemingly gone awry in our time—we are disquieted. Patients seem unhappy, physicians are unhappy, government is unhappy, and both patients and physicians feel disenfranchised and afraid. Patients say that medical care is impersonal, hurried, expensive, and fragmented; physicians fear lawsuits and harassment, even murder. Physicians tell their daughters and sons to do anything but medicine, and some patients trust their pharmacists more than they do their physicians. Why?

A lot of things can be blamed: rising patient expectations with inevitable disappointments; technology, worker of miracles, but sterile and mechanical; mounting bureaucratic regulation and paperwork; a society that asks medicine to solve more problems than it is competent to do, allied with physicians who in promising wellness may have exceeded their ability to provide it. We are also troubled with some lawyers, not all, who confound both physicians and patients with nuisance suits.

And physicians have gone wrong, some of us, who forgot the core of the oath and became accustomed to, even demanding of, medicine that the career provide first for the fulfillment of our professional and personal needs. This sense of physician entitlement grew upon us insidiously over the past affluent quarter century: physicians studied hard, worked long hours, achieved much, had families to support, and did good things—including considerable charitable care. And if we could do all this and prosper, what was the harm?

Joseph Campbell, in his book, *Hero of a Thousand Faces*, tells the story of King Minos of Crete who, when contending for the throne, prayed to Poseidon to send him a sign of his divine right to rule–a white bull born of the foam of the sea. And if he became king, Minos vowed, he

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would sacrifice the bull back to the god of the oceans as a symbol of service. Poseidon sent the animal, and Minos, visibly favored by the god, was crowned. But, enraptured by the splendor of the beast, he kept it.

Minos was a wise ruler, and Crete prospered, became a busy, rich mercantile center, and was the model city of the ancient world. But in the bowels of the palace a monster was born, son of the gift bull. It had the body of a man and the head and tail of a bull—the Minotaur. As it grew, it demanded more and more of the children of Crete as offerings. So, though he seemed successful, Minos was cursed by the people. He had created evil because he had, for personal gain, betrayed the whole sense of his investiture, which was that, as king, he was no longer a private person, but one obliged by his vow to sacrifice—to give back—the sea gift that put him on the throne.

Now we physicians, through our oath, have made a vow, too—but perhaps because of the natural desire to keep the gift of trust, respect, and status given us by our patients, we have taken it for granted that it is ours. This may have bred our Minotaur.

All of us want to be worthy, to know that we are valued, but the criteria for worthiness in this country appear to be preeminently two: how much control we have over our own lives and how much we earn. The problem is, of course, that control of our lifestyle and how much we make is now confronted by the reality of our time—a nation of patients who want other kinds of physicians than we may want to be, and who have less money to give us for our services.

As we listen to physicians discussing the problems of health care reform or read editorials on the maldistribution of physicians or the decline of generalists, some solutions proffered by medical experts appear to be self-serving: Does the American public want more generalists? Then pay them more! Want more rural physicians? Give them a better lifestyle! Want more women and minorities in medicine? Make it worth their while! The American public, hearing this, has every reason to question our motives.

Most physicians are not venal. It is not really the money, in most cases, that propels them in their work. Most physicians would not mind cutting their incomes—but only if everybody else does, too. What does disturb physicians is that other professions or other specialists in our profession make more money than we do, particularly if we think we work harder than they do. It enrages us that a plumber makes more per hour than a family practitioner or that a 15-minute technologic procedure is paid better than an hour of intensive interpersonal care with a patient. But why does this bother us so? Even the poorest paid physicians make over two times the average national salary, and most of you will make more. Frankly, it is a good living, especially in these hard times. But it galls us because most physicians have accepted the American equation that money equals respect, and we all want to be respected. So it is not greed that drives this emphasis on money so much as it is pride. But—and here lurks the Minotaur—the acceptance of the idea that the more physicians are paid, the more valuable they are not only spirals costs, but is pernicious. If money and control represent status to physicians among physicians, then it is hard not to simultaneously believe that the worth of our patients can also be judged by how much money and control they have. This is iniquitous.

Perhaps some of this concern with money and management is a product of a well-meaning effort to be modern and "politically correct." Wordsmiths began about two decades ago to craft new names for patients (patient is derived from the Latin, meaning "those who suffer"). "Power-giving" titles for patients were drawn from the world of commerce: they became customers, consumers, clients, purchasers. Medicine became the health care industry, physicians became health care providers. But this is all wrong.

A hungry man may go to a grocer, but having no money for food is turned away. A pity, but that is the way of custom.

A homeless woman asks a landlord to let her live rent free and is refused. We are not even mildly shocked, except at her audacity.

An ill-clad family is cold and needs clothes, but cannot pay for them: these department store purchasers get nothing without money.

But if a sick person appears in a physician's office or emergency department and is refused care because of poverty, we are repulsed. Why?

Because physicians are supposed to be better than that!

Medicine transcends mercantilism: no grocer, landlord, or merchant is sworn to help the hungry, homeless, or naked as the purpose of their lives. If they do help, it is by charity. Physicians are sworn to help the sick by obligation. The suffering are not customers, consumers, purchasers, or clients—they are patients, with whom we have a covenant.

So when we speak of our right to an acceptable lifestyle and salary, we have made the mistake of Minos. We want to have both the gift of our status as private persons and our investiture as physicians. Now we appear to have come to a time where we have a choice, but may no longer have both.

So when you take the physicians' oath, consider carefully what you are saying. You are not promising to be paupers or saints, but you are promising sacrifice in that if you cannot have it all, you will choose for the well-being of your patients above your comfort, your control, your pride. Are you willing to do this, for the privilege of being allowed to do the most interesting and gratifying work in the world?

I think that many are, but it will be easier if we can rid ourselves of the bitterness generated by the conviction that to take less means that we are worth less in society or in medicine. We must, in order to be happy, believe that, for physicians, the work itself is what is rewarding. Your value as a physician depends on what you give, not what you get.

You are our best hope, ever. Your generation came to

medical school at a time when you were discouraged by a chorus of naysayers who told you not to do it. You were told that you would go deeply into debt, struggle with red tape, hold lower social status, have decreased autonomy, and be the creatures of the system rather than its masters. And you said "Nonetheless, I want to be a physician." And if you were telling the truth, you will keep your vow, return the gift, and be the richer for it. Not in material things, perhaps, but in the important things. At the end of their career, the better paid plumbers will reflect on pipes. Physicians will have the kaleidoscope of memories of birth and death, happiness and despair, discovery, courage, intellect, humor, intimacy, elation, and service. These are the enduring riches of a physician's life. You will make a living, but, more important, you will have lived.

I wish you well.

* * *

GOING BACK

how do I message your machine
it's fifty years ago today
on the soft green fields above the Hudson
this Brevet Colonel of the United States Armed Forces
struck a cleat so deep
with mud above my right eye

that years later
the first husband of Ingrid Bergman
who was trained to wire and screw teeth
but switched to neurosurgery
had to ronger out all the bone and fashion

a metal plate with fine bolts
into my one temple
removing a huge skull tumor
and part of that same cleat
in order to cover up
an exposed brain.

Anyway it's Saturday morning again
when I'm required to go
yell and work up headaches
headaches over my children
playing at games of soccer to the Beach Chalet

where nobody believes I have
this metal screwplate in my head from
half a century when I scored
the winning goal against them
allmale jocks at West Point

and my team threw cold water on me
as everybody did then to wake you up
and hoist me high on their shoulders
and ran around that field shouting triumph with me
held so high to show those guys we won and
they could never kill anybody like us like that anymore.

so when the hard pains began from babies
tap tapping on my forehead
probing love in my mind's eye
I remember my sainted father
who was an ace pilot in France
with the 50th Aero Squadron in the First World War

saying everybody now was going to wear medals
when the Nazis overran Europe
so he sent to collect his Silver Star and wore
it secret behind his lapel which he could turn out
to show dodgers on the street—
suddenly I had to own mine too, and years later
sent for and sutured lovingly with silk
my big orange **P** just for Saturdays like this.

But when you go ask them after their game
to feel the screw in your head they laugh
say yuk and don't believe
except once in my new sweater at the airport
taking them back to show off my old college room
I couldn't pass the metal detector test
they listened and wondered why

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Editorials

HTLV-II Infection in the Western United States

RETROVIRUSES are the first known transmissible oncogenic agents. Peyton Rous recognized the first oncornavirus at the turn of the 20th century, when he identified a filterable agent that caused transmissible sarcomas in chickens.[1] The discovery of human T-cell leukemia or lymphoma virus type I (HTLV-I) represented the culmination of a prolonged and frustrating effort to identify a human counterpart to oncogenic retroviruses of birds and rodents. This retrovirus was first isolated from a patient with a cutaneous T-cell lymphoma.[2]

Human T-lymphotropic virus type I has properties that render it distinct from either of the two previously described RNA tumor virus groups. Like the chronic RNA tumor viruses, HTLV-I induces a clonal malignant neoplasm (adult T-cell leukemia or lymphoma) after prolonged latency. Like the acute RNA tumor viruses, HTLV-I unilaterally transforms cells in vitro to a malignant phenotype. These novel properties of HTLV-I can be ascribed, in part, to a weakly oncogenic replicative gene known as *tax*.[3] A simian version of HTLV-I, known as STLV-I, is widespread in Old World primates.[4]

By the mid-1980s, it was appreciated that HTLV-I was also responsible for a chronic, debilitating paralytic illness known as tropical spastic paraparesis or HTLV-I-associated myelopathy (TSP/HAM).[5,6] The collective risk of adult T-cell leukemia or lymphoma or TSP/HAM in HTLV-I-seropositive patients is low but not negligible. Depending on the age at which HTLV-I is contracted, the risk of either a fatal malignant disorder or progressive neurologic disease developing is about 2% to 6%.[3]

The endemism of HTLV-I is highly focal. High seroprevalence is found in southwestern Japan, in regions populated by the descendants of west African slaves (the Caribbean, Brazil, the southeastern United States), in sub-Saharan Africa, and in Iranian Jews.

In late 1988, the United States Food and Drug Administration (FDA) approved an enzyme-linked immunosorbent assay to screen blood donors and others for HTLV-I antibodies.[7] Screening was instituted immediately by all US blood banks. Western blot confirmatory assays were developed, although none are yet FDA-approved.[8,9] A wealth of seropositive blood donors was soon identified. Epidemiologic correlates to HTLV-I seroprevalence were discovered. Injection-drug users, certain ethnic minorities, and transfusion recipients (but not homosexual men) were found to have an increased risk for HTLV-I.

There was already a fly in the ointment. Workers were noticing two distinct and specific Western blot banding patterns among donors considered to be HTLV-I-seropositive.[8] One pattern, similar to that seen in known HTLV-I-seropositive persons in Japan and the Caribbean, predominated in the eastern United States. Another pattern was predominant in the West. Some investigators considered that this pattern could be due to HTLV-II, a relative of HTLV-I. At first this seemed unlikely. As of 1989, only 7 persons were known to be infected with HTLV-II.

Using the polymerase chain reaction, researchers showed that HTLV-II was not rare and obscure, but was in fact the predominant retrovirus in "HTLV-I"-seropositive users of injection drugs.[10] This surprising finding was confirmed in subsequent studies of western US blood donors.[11] Most seropositive western blood donors were found to be infected with HTLV-II. By contrast, seropositive blood donors from the eastern states are usually infected with HTLV-I.[11,12] Most HTLV-I-seropositive donors had a link to a known area of endemic HTLV-I infection, such as Japan.

What, then, was the source of the western focus of HTLV-II? This remains unknown. The virus comes in two distinct variants, known as HTLV-IIa and -IIb.[13] These two viruses differ by 3% to 4% at the nucleotide sequence level, translating to a difference of but 1.5% to 2% at the protein level. Although the difference is small, the HTLV-IIa and -IIb viruses represent highly discrete and distinctive forms of HTLV-II. There are no intermediate forms. Both forms of HTLV-II can be identified among contemporary injection-drug users.[13] The source of HTLV-II must thus encompass both forms if western HTLV-II endemism is indeed to be ascribed to a single source.

Of those groups with no identifiable parenteral risk for HTLV infection, New World Indians have the highest HTLV-II prevalence.[14-16] The highest HTLV-II prevalences by far occur in certain remote Indian tribes.[16] New World Indian groups appear to be host to both HTLV-IIa and HTLV-IIb.[17] Blood donation is common among members of some of these tribes. Such donations, made before blood banks instituted HTLV-I antibody screening, have resulted in the transmission of HTLV-II.[3] Although some unexplained African foci of HTLV-II exist, it appears that HTLV-II is essentially a New World counterpart to HTLV-I. That concept is strengthened considerably by the recent discovery that New World monkeys are host to an HTLV-II-like simian virus known as STLV-II.[18]

The findings of the study by Hanne Thiede, DVM, MPH, and colleagues reported elsewhere in this issue of the journal, offer additional support for the concept of an old, widespread, and entrenched HTLV-II endemic focus in injection-drug users.[19] Other studies have shown that HTLV-II-infected persons have been present among urban injection-drug users since at least the mid-1970s.[20] With seroprevalences that dwarf those of the human immunodeficiency virus (HIV) and that increase with age, the King County study suggests that HTLV-II is endemic and mature in Washington State injection-drug users. If anything, the authors may have underestimated the prevalence of HTLV-II in their study population. Many HTLV-II-infected subjects have HTLV-II antibodies that go undetected in the HTLV-I enzyme-linked immunosorbent assay.[21,22] Furthermore, Thiede and co-workers insisted on

the demonstration of antibodies to HTLV-I gp 46 or gp 63 in their confirmatory definition of seropositivity. Such antibodies are often absent in subjects with HTLV-II infection (unpublished data, 1992).

The largest remaining question concerns the clinical import of HTLV-II infection. This is a difficult question, in part because the known worldwide burden of HTLV-II infection is small compared with that of HTLV-I. Many populations with high HTLV-II prevalence are small and geographically remote.[16] Others, such as injection-drug users, are unstable and prone to other serious health problems such as HIV infection. It has proved difficult to show definitively that HTLV-II is responsible for human disease. The first HTLV-II organisms identified were derived from patients with atypical T-cell malignant disorders with some features of hairy cell leukemia.[23,24] Other isolated organisms have been derived from patients with large granular lymphoma or mycosis fungoides.[25,26] Epidemiologic investigation has failed to demonstrate any increased rate of lymphoid malignancy in populations with high HTLV-II prevalence or to identify increased HTLV-II prevalence in patients with lymphoid malignancy.[14] A number of patients with TSP/HAM-like neurologic disease have been identified among those with HTLV-II infection, however.[27-32] Despite this suggested association between HTLV-II and TSP/HAM, neurologic disease is apparently a rare consequence of infection with HTLV-II.

The identification of any new population with high HTLV-II prevalence is welcomed by researchers interested in possible pathogenic effects of this virus. Perhaps the substantial group of HTLV-II-infected subjects in King County will be large enough—and stable enough—to contribute to a definitive longitudinal study that will show that HTLV-II does or does not cause disease.

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What Columbus's Voyages Wrought

RECENT EVENTS surrounding the celebration of America's quincentenary have forced historians on both sides of the Atlantic to reexamine the ideologic foundations of earlier views of the highly touted and now politically incorrect "discovery" of the "New World." Instead, politicians and intellectuals have adopted a perspective recently articulated by, among others, Mexico's renowned scholar Miguel Leon-Portilla. To characterize the first contact and subsequent colonial process, Leon-Portilla employed the Spanish word *encuentro* ("encounter") to convey the meanings of collision, conflict, and opposition, but also approach, convergence, and linkage between the various cultures representing the Old and New

Worlds.[1] As another author declares, "Encounter has much to recommend it. Encounters are mutual, reciprocal two-way rather than one-way streets."[2(p35)] Such a reframing of the historical perspective demands a new conceptual scaffolding that takes into account all participants of the colonial enterprise along a broad spectrum of activities, from violent confrontation to peaceful fusion.

One of the most dramatic stories of the Columbian encounter, presented elsewhere in this issue of the journal by Carlos A. Camargo, MD, focuses on the immediate exchange of diseases between the arriving Europeans and the Native Americans who inhabited the Caribbean islands.[3] Our understanding of the lethal effects of this conjunction has finally permeated to the public at large. While the stark reality of successive and devastating epidemics decimating the indigenous populations is now widely accepted, demographers, historians, and epidemiologists remain divided about the scope and rate of human destruction and its causes. Much has been written recently on the demographic collapse of indigenous American populations, a highly politicized subject wherein estimates diverge widely.

In recent years, scholars in this field of inquiry have stressed the interdisciplinary nature of the enterprise and the fragmentary evidence hitherto uncovered to document the main events. Camargo subscribes to the widely held notion that the catastrophe was generated by a number of "virgin soil" epidemics, accepting the proposition that the native inhabitants of America possessed no immunity to most infections arising from the European and African disease pools. He thus identifies a number of conditions, from swine influenza to smallpox, that in successive epidemic waves proceeded to decimate the original population until their virtual extinction forced a generation later the unprecedented importation of slave labor from Africa.

Such identifications, now made centuries later on the basis of incomplete information, remain difficult and tentative. Smallpox, of course, may be an exception because its typical manifestations facilitate a plausible retrospective diagnosis. The same, however, is not true for measles and typhus. From the surviving evidence, it becomes clear that several epidemic outbreaks consisted of more than one disease, forming "compound epidemics." Regarding disease transmission, we must await more detailed regional studies to obtain a better picture of the dynamics of European colonial penetration.

To explain this disaster, biologic susceptibilities in the American natives are stressed. Much has been made recently about their genetic uniformity and immune incompetence. It is said that their slow trek across the existing Bering landmass more than 30,000 years ago functioned as a biologic selector and "cold screen" that eliminated harmful bacteria and viruses from their bodies. Moreover, the lack of larger-sized animals available for domestication on this continent also shielded the new Americans from recurring zoonoses all too often shared with their human owners in other parts of the globe. Thus, we are persuaded to conclude that the vaunted El Dorado may have been more a disease-free rather than a gilded environment, a notion in harmony with romantic views of noble and vigorous savages freely roaming the vast plains of the New World.

While it is proper to highlight the biologic components of the massive die-off of American natives, one must not understate the equally important social factors that contributed to such a string of deadly epidemics. Initially the aggressive conquerors practiced a "scorched earth" policy that caused widespread environmental damage and social disorganization. Like recently in Somalia, large numbers of displaced refugees with severe nutritional deficits wandered aimlessly through the countryside starving to death. Their culture condemned as the product of Satan, natives became disoriented, depressed, and suicidal. Although debilitated in body and soul, many were forcefully herded into new farming schemes such as the *encomiendas*, where alcoholism took an additional toll on their already precarious health. Other urban resettlement plans only reinforced substantial crowding and lack of hygiene, providing further human fodder for the epidemics. To truly unravel the "web of disease" is to include factors such as warfare, sanitation, and transportation in the epidemiologic context.

Reflecting the new historiographic direction, Camargo goes to some lengths in presenting a balanced view of the Old and New World medical systems. One was represented by professionalized European physicians and surgeons with their Galenic humoral system, the other by a variety of tribal folk healers with equally comprehensive explanatory schemes and command of an impressive variety of local medicinal plants. Indeed, it was their similarity rather than contrast that deeply impressed the first settlers and recent historians. Both medical systems were linked to cosmic views that emphasized magical explanations of natural events while considering humans as small replicas of the universe. Each group explained bodily phenomena in health and disease through the actions and balance of humors, and each tried to maintain health through prescriptions of an ordered lifestyle and adequate nutrition. In European and Nahuatl medicine, these humors were thought to be in some form of quantitative balance and to possess a number of intrinsic qualities, including cold, hot, and moist, that made them susceptible to physician-initiated adjustments in the event of disease.

European physicians carefully inspected the sick, attempting to determine their physical constitution within the traditional Galenic model. Given their white complexion, Spaniards were usually categorized as cold while the natives were considered hot, choleric, or melancholic. A person's relative girth provided the second essential quality, with thin people tending to be dry and the more robust humid. Operating within such a basic body typology, healers were enjoined to observe the alterations brought about by illness and urged to prescribe foodstuffs and medication endowed with opposite qualities to reestablish a balance. A similar calculus of bodily fluids and their qualities was accepted among the tenets of Nahuatl healing in Mexico. Thus interpreted, the salient symptoms provided the groundwork for an individualized interpreta-

tion of disability within the framework of European and native humoralism.

In both societies, healers played important roles in dealing with sickness. Magical and religious ceremonies were common, including the use of amulets, prayers, and in the case of Europeans, the action of relics. Such activities coexisted with empirical problem-solving techniques, including wound healing, a necessary first-aid skill in societies constantly engaged in warfare. Other purification routines such as sweating and bathing, common to both native and European cultures, were usually available, including native hot vapor baths or *temascales*. In the area of healing plants, the New World provided a veritable bonanza in its extraordinary, diverse ecologic niches.

Another consequence of the Columbian encounter was the establishment of European-style hospitals in the New World, institutions without American counterparts. Conventional histories of the European-American transfer of institutions often describe early colonial hospitals as charitable foundations established by enlightened rulers or local town councils to ensure the provision of medical care for both Spaniards and natives in the face of widespread disease. What is less known is that, given their small size and limited resources, these hospitals actually played a minor role in the service of the sick. Indeed, although millions of New World inhabitants perished, only a few hundred found shelter and care in such establishments. Even if their importance as centers of medicine was negligible, these institutions constituted an early and unique contact point between two distinct medical cultures.

In New Spain and elsewhere in the colonies, the presence of native healers, who employed an array of local plants with medicinal qualities hitherto unknown to the Spaniards, added notably to hospital care. This was especially true in those institutions dedicated to the native population. Here both healers and patients could continue to build relationships based on shared paradigms of health and disease. Local preparations replaced the traditional and costly Old World armamentarium of purgatives, analgesics, diuretics, and stimulants used for symptomatic control. A second edition of Lopez de Hinojoso's *Suma*, published in 1595, promoted the use of more than 50 such native herbs, based on Lopez's experience at the Hospital Real de los Naturales. The same can be said of another book, *Tratado Brebe de Medicina*, published in Mexico City in 1592 by another Spanish physician, later an Augustinian friar, Agustin Farfan. Readily available, these products were prepared as powders, syrups, wines, infusions, and ointments and widely administered to the sick. Hospitals thus provided small but controlled populations for clinical observation and experimentation.[4]

When the Spanish *protomedico* Francisco Hernandez visited the Hospital de Santa Cruz around 1574, he was able to learn a great deal about these healing herbs, returning to Mexico City with a rich harvest of information concerning their pharmacologic actions. Searching for care of his impaired health, Gregorio Lopez, a hermit and author of *Tesoro de las Medicinas*, had a similar experience at that institution. A lack of precise measuring techniques and standardized preparations of such plants may have created variations in dosage that prevented a clear delineation of their clinical effects.[5] Thus, a vigorous program of clinical experimentation initiated by Franciscan and Augustinian friars and Spanish physicians sought to improve on the therapeutic indications and helped to highlight the efficacy of a number of important plants.

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Familial Benign Hypocalciuric Hypercalcemia—From the Clinic to the Calcium Sensor

In 1972 Foley and co-workers described a new familial hypercalcemic disorder that they called familial benign hypercalcemia,[1] emphasizing the asymptomatic nature of the condition. Additional affected families were described by Marx and associates, who preferred the rubric familial hypocalciuric hypercalcemia for the disorder.[2] All of the essential clinical features were described in the original reports. Despite lifelong hypercalcemia—which can first be detected in cord blood—persons with familial benign hypercalcemia are protected from the development of kidney stones, bone loss, and other consequences of sustained hypercalcemia. The disorder is heritable as an autosomal dominant trait with high penetrance, affecting 50% of members of affected families. The other biochemical features include low-normal or decreased concentrations of serum phosphorus, mild hypermagnesemia in about half of patients, and the characteristic relative hypocalciuria in the face of an increased filtered load of calcium. Unfortunately, both terms, familial benign hypercalcemia and familial hypocalciuric hypercalcemia, are still in use as rubrics for the disorder. It seems best to combine them into a single designation, familial benign hypocalciuric hypercalcemia (FBHH), as I have done here.

As discussed in detail by Heath elsewhere in this issue of the journal,[3] it was clear from the beginning that FBHH is an atypical form of hyperparathyroidism. The parathyroid glands are normal or slightly increased in size. With the use of modern assays for intact parathyroid hormone (PTH), which are sensitive and specific enough to detect the suppression of PTH in nonparathyroid hypercalcemia, the serum concentration of PTH in FBHH is generally in the high-normal range, inappropriate for a person with

hypercalcemia. In about 20% of patients, the level of intact parathyroid hormone is increased, to as much as 8 pmol per liter (80 pg per ml).[3] Most strikingly, persons with FBHH have an atypical response to parathyroid surgery. Often subjected to parathyroidectomy because of confusion with typical primary hyperparathyroidism, these patients resist any attempt to restore normocalcemia by subtotal resection of parathyroid tissue. Within a short time postoperatively, their serum calcium level has invariably returned to the previous range, but they are rendered hypocalcemic by total parathyroidectomy, confirming the parathyroid dependence of their hypercalcemia.

In the article that first described FBHH, these features led to a prescient conclusion about its cause. "Rather than an excessive primary secretion of parathormone, an inappropriate requirement of an unusually high concentration of calcium to suppress the production of parathormone better explains the abnormal pathophysiology."[1(pp1064-1065)] Subsequent clinical studies supported this notion that FBHH is typified by an inborn calcium-sensing error, an increased "set point" for the physiologic suppression of PTH secretion by calcium.

The calcium-sensing mechanism of the parathyroid glands has now come under molecular scrutiny. Taking advantage of the ability to confer calcium sensing on *Xenopus* species oocytes by administering parathyroid messenger RNA, Brown and colleagues recently used expression cloning to identify a parathyroid calcium sensor.[4] The cloned protein appears to be a member of the family of G protein-coupled receptors, with a large extracellular region of 605 amino acids linked to a serpentine G protein-activating domain predicted to span the plasma membrane seven times. The gene for the parathyroid calcium sensor is located on chromosome 3,[5] near the previously reported locus of the most common FBHH gene.

The same group who identified the parathyroid calcium sensor has now shown that point mutations in the sensor are inherited in FBHH.[5] Two of the mutations identified to date are in the large extracellular domain, already thought to bind calcium because of its resemblance to a family of bacterial binding proteins that bind ions and small inorganic molecules in the periplasm. The one FBHH mutation that has been expressed induces attenuated calcium signaling in *Xenopus laevis* oocytes, consistent with the FBHH phenotype. Thus, the molecular pathogenesis of FBHH has been elucidated.

Viewed as an experiment of nature, the FBHH phenotype makes several predictions about the calcium sensor. The hallmark finding of hypocalciuria in FBHH is probably an intrinsic property of the kidney because it persists after total parathyroidectomy[6]; thus, it must be the calcium sensor that sets the level of urinary calcium excretion. Indeed, the newly identified calcium sensor is strongly expressed in renal tissue. The sensor must also be involved in setting the level of serum magnesium, perhaps also at the renal level. It is conceivable as well that the remarkable tolerance of these persons to lifelong hypercalcemia is due to blunted sensing of the serum calcium level in other tissues. The implication that many tissues can sense changes in extracellular calcium, together with the likelihood that there are other members of the calcium sensor family that respond to other extracellular ions, raises the possibility of a new type of metabolic regulation, in which surface receptors allow cells to sense and respond to changes in their ionic milieu. As has so often been the case in the past decade, the meticulous clinical investigation summarized in this issue by Heath, combined with molecular genetics, has opened up a new vista of biologic regulation.

A rare syndrome of neonatal severe hyperparathyroidism sometimes occurs in FBHH families. The molecular genetics of this disorder now show clearly that severe hyperparathyroidism of neonates is the homozygous state of the FBHH mutation, again confirming the conclusion of clinicians. Thus, a calcium-sensing abnormality, when severe, leads to massive hyperplasia of the parathyroid glands. The cloning of the calcium sensor provides the means to begin to study the interrelation between the two classical responses of endocrine tissues to a homeostatic challenge: the immediate secretion of hormone and hypertrophy of glandular secretory tissue, which amplifies the secretory reserve. In about two thirds of typical parathyroid adenomas, the secretion of PTH is suppressible by high levels of serum calcium. Perhaps somatic mutations that give rise to abnormalities of calcium sensing are oncogenic in these parathyroid adenomas, as they appear to be in neonatal severe hyperparathyroidism.

Clinicians faced with the task of distinguishing FBHH from typical asymptomatic primary hyperparathyroidism rely on the family history and biochemical determinations of PTH, urinary calcium, and serum magnesium. This task is not always easy, however. The ranges of all the biochemical indices in FBHH and primary hyperparathyroidism overlap, and the opportunity to screen family members for asymptomatic hypercalcemia is often crucial to the diagnosis. Happily, clinicians who are vexed by a patient without an available family can now look forward to the diagnosis of FBHH by molecular genetic means.

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HIV Infection in Women

To the Editor: In California reproductive-age women account for an increasing proportion of newly diagnosed cases of the acquired immunodeficiency syndrome (AIDS).[1] To effectively allocate resources for prevention, care, and treatment of these women and for AIDS orphans, health care professionals must be aware of the geographic distribution of infection with the human immunodeficiency virus (HIV) in women.

Using data from a federally funded survey of HIV infection in childbearing women,[2] we examined the demographic and geographic distribution of HIV type 1 infection in the third quarter of each year from 1988 to 1992 among women who gave birth to live infants. We grouped the county of residence information into urban or nonurban regions (Figure 1) based on the following variables: population density, median family income, number of housing units per square mile, ratio of physicians to residents, and the proportion of county land designated as rural.[3]

Of 727,325 women with live births recorded in the period under review, 520 were confirmed seropositive, representing an overall prevalence of 7.1 per 10,000. Table 1 shows the differences in prevalence of HIV infection in urban and nonurban regions. The cumulative prevalence in the urban regions (8.2 per 10,000) is more than twice that in the nonurban regions (3.9 per 10,000). In the urban regions, the observed prevalence among women from the Bay Area counties of Alameda (21.2 per 10,000), San Francisco (20.0 per 10,000), and Contra Costa (14.2 per 10,000) was higher than that in other counties in California. Within the nonurban regions, the eight-county San Joaquin Valley area—Fresno, Kern, King, Madera, Mer-

Figure 1.—The map of California shows urban (shaded) and nonurban counties.

TABLE 1.—*Demographic Characteristics of Childbearing Women (n = 727,325) and Year of Test by Urban and Nonurban Classification*

	Women in Urban Regions				Women in Nonurban Regions			
Characteristics	*No. Tested*	*No. Positive*	*Rate/ 10,000*	*95% CI*	*No. Tested*	*No. Positive*	*Rate/ 10,000*	*95% CI*
Age, years*								
<20	55,631	39	7.0	5.1-9.7	23,535	5	2.1	0.8-5.3
20-24	126,993	114	9.0	7.4-10.8	47,009	24	5.1	3.3-7.7
25-29	150,466	127	8.4	7.1-10.1	48,934	17	3.5	2.1-5.7
30-34	113,994	81	7.1	5.7-8.9	32,424	14	4.3	2.5-7.4
≥35	57,654	38	6.6	4.7-9.1	15,486	4	2.6	0.8-7.1
Total		399				64		
Race or ethnicity†								
White	190,494	88	4.6	3.7-5.7	85,924	23	2.7	1.7-4.1
Black	44,941	198	44.1	38.2-50.7	8,589	22	25.6	16.5-39.5
Hispanic	232,733	125	5.4	4.5-6.4	69,202	21	3.0	1.9-4.7
Asian	34,509	6	1.7	0.7-4.0	5,890	0	0	0
Other	39,472	26	6.6	4.4-9.8	9,549	2	4.2	0.4-8.4
Total		443				68		
Year of test								
1988	100,999	92	9.1	7.4-11.2	30,312	8	2.6	1.2-5.4
1989	107,291	77	7.2	5.7-9.0	32,278	12	3.7	2.0-6.7
1990	112,261	91	8.1	6.6-10.0	38,233	15	3.9	2.3-6.6
1991	114,975	104	9.0	7.4-11.0	39,943	20	5.0	3.1-7.9
1992	111,644	86	7.7	6.2-9.6	39,389	15	3.8	2.2-6.4
Total		450	8.2			70	3.9	

CI = confidence interval

*Information is missing for 51 and 6 seropositive women in urban and nonurban regions, respectively.
†Information is missing for 7 and 2 seropositive women in urban and nonurban regions, respectively.

ced, San Joaquin, Stanislaus, and Yolo—had the highest prevalence (5.1 per 10,000), accounting for 50% (35 of 70) of all seropositive women but only 38% of the total number tested. While the prevalence of infection in the urban regions declined slightly from 9.1 per 10,000 in 1988 to 7.7 per 10,000 in 1992 ($P = .77$), the rate in the nonurban regions increased from 2.6 to 3.9 per 10,000 ($P = .30$) in the corresponding period. In both regions the crude prevalence of infection among nonwhite women was higher than that among white women. Although nonwhite women accounted for about half (52%; 94,231 of 180,155) of those tested in the nonurban regions, they were overrepresented among seropositive mothers (67%; 47 of 70). Among young mothers (<25 years old) in the nonurban regions, white women had a higher prevalence (4.8 per 10,000) than nonwhites (3.6 per 10,000) ($P = .43$). In the other age groups, however, nonwhite childbearing women in both regions show significantly higher prevalence rates of HIV infection than do white women.

These results indicate that HIV infection among women is not confined to urban areas of California. Cases of AIDS due to heterosexual contact and injection drug use are increasingly being diagnosed in the nonurban areas of the state.[4,5]

In response to this trend, the California Department of Health Services Office of AIDS provided funding for education and prevention programs in some nonurban areas through the HIV Education and Prevention Rural Initiative. Nonurban counties reported about 5% of the total 67,352 cases of AIDS reported through December 1993 and received about 15% of the available state funds ($15.8 million) for HIV education and prevention. In addition, all agencies that provide HIV prevention services in nonurban areas have direct access to the AIDS Hotline, the California AIDS Clearinghouse, training, and other programs funded by the Office of AIDS.

Recognizing the unique challenges faced daily by nonurban communities in identifying and reaching persons at risk of contracting HIV, the Office of AIDS adopted an innovative HIV prevention approach. This approach differs from that used in urban communities where agencies are funded to provide services to Office of AIDS-defined target populations such as men who have sex with men or substance abusers. Under the rural initiative, local health departments and community-based groups define the target populations of local concern. Thus far, most of the agencies funded by the Office of AIDS under the rural initiative provide services to at-risk women, substance abusers, and youths.

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Requiem for Medicine?

To the Editor: The impassioned essay by D. Gordon Johnston, MD, "Death of a Doctor," reveals not only his anguish, but also apparently how far he is from the current state of medicine.[1] I note that he is now a full-time writer.

Medical care today is a battleground. Physicians are caught in the middle, presumed by all sides to be the enemy. We have become targets of all who would criticize, victims of needing to follow a course through a minefield of risks. We constantly dodge assaults. We bleed from many wounds of constant skirmishes with insurance companies. We cower in the trenches, striving to fight disease, but struggling more to stay alive in the battle zone. How can we be asked for compassion, sympathy, empathy?

DRGs [diagnosis-related groups] care not about compassion. CPT [Current Procedural Terminology] codes have no category for sympathy care. ICD-9 codes know nothing of empathy. Insurance companies do not seek to understand the art of health care to humans. They seek rather to lay traps so that an unsuspecting patient will fall into the category of "uncovered services." Medicare does not care that a physician has a patient return because the family was frightened and wanted another visit. Medicare, rather, seizes the opportunity to look for "concurrent care" so that the physician can be upbraided for failing to discover that some other physician has submitted a bill for that day with the same diagnosis on it. So if we see the flower of altruism wilted and dying, know that it succumbs to the poisonous atmosphere of the battleground.

Yet, when we bemoan the current state of health care, we are focusing on nothing more than a symptom. The illness is much broader. America is in grave trouble. We have lost our moral underpinnings. We are building a country without a soul: unguided by honor, a country of the "not responsible," of regulations rather than of ethics, of cold technology, of lawyers who function as social mercenaries—for hire to any cause, to attack whoever may fall profitably, inadequately restrained by conscience and social responsibility.

Our society is at war with itself, committing slow suicide in the anguish of its disparate expectations and on its way to becoming a carcass. It is dying from its loss of solid values, of clear leadership, shared responsibility, and sufficient collective wisdom to resolve our dilemmas with technocracy. We are driven to desperation. We want all that technology can provide, but do not want to pay the price, and we do not know how to support humanity amid technology.

We cannot treat well the symptoms of our illness without treating the disease. We cannot resolve our dilemmas

by battering physicians simply because they fail to save us from our philosophical impasse. On this course we shall only lay waste to the medical profession and kill the soul that once gave it compassion and altruism.

But, alas, we will not treat the disease. It is too easy to look for scapegoats. We will not have the courage to be strong, because weakness is easier. We will not take up the yoke of responsibility because irresponsibility is easier. We will not have true leaders because they must be willing to say what is unpopular. Rather, we will delude ourselves that the shiny trappings of our technology shall make up for our withered soul. We shall go on to slow suicide, afraid to raise our collective philosophy to meet the challenges of technocracy.

And the world will look elsewhere for its 21st century leader. America has had her day. What Dr Johnston wants from physicians, and what we once had to offer, was the product of a different social environment. Requiem.

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REFERENCE

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* * *

Dr Johnston Responds

To the Editor: I appreciate Dr Barbuto's comments relative to "Death of a Doctor" and his incisive, articulate review of not only the current deplorable abuse of physicians by our health care system but also the crisis of decline of the ethics, morality, and responsibility of our citizens and our leadership.

I agree with most of his observations and share his distress over the nearly intolerable conditions under which physicians are expected to serve. On the other hand, physicians must not reject their responsibility to provide humane, compassionate care for those accepted into their practices. For a physician to abandon that responsibility to the sick and injured is an affirmation that it is OK to be irresponsible.

When a physician can no longer tolerate the unfair treatment and persecution from the entities so well enumerated by Dr Barbuto and can do nothing to correct those abuses, that physician can leave medicine and do something else, as I have done.

I would add one other adversity for physicians in some areas: hospitals engaged in pressuring physicians to join hospital-owned provider plans—physicians essentially becoming hospital employees. Other hospital activities include using referral lists to pressure physicians to refer patients to hospital-owned outpatient services and discriminatory surgical scheduling favoring surgeon tenants of office buildings owned by hospitals.

Every physician, however he or she may react to adversities of practice, must continue to provide competent and compassionate care to patients.

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Financing Long-term Care

To the Editor: In the article "Paying for Long-term Care" by Estes and Bodenheimer in the January 1994 issue,[1] I think the authors have misunderstood the essence of financing long-term care. The ultimate result of financing long-term care and not requiring people to "spend down" to obtain this care, as is presently done, is that we are providing an inheritance for their children. I do not think this is in the public's interest. The principal inequity of our present system is, of course, that a spouse is also impoverished by this "spend-down" procedure. That could be more adequately addressed by allowing the spouse to retain a certain amount of assets for the rest of his or her life with the provision that these assets then go to the state and not to an inheritance.

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REFERENCE

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* * *

Dr Bodenheimer Responds

To the Editor: We appreciate the excellent point made by Dr Hann. We do not entirely agree with it, however. The spending of tens of thousands of dollars in savings represents a major financial threat to elderly people themselves, not simply to the inheritances of their children. Many retired people supplement their social security or pension incomes with interest and dividends on their life's savings or see those savings as an important form of financial security.

Dr Hann is correct that society has no obligation to ensure that children will receive an inheritance. But there is a randomness to the need for long-term care that allows the children of parents who die suddenly to receive a large inheritance while children of parents who require years of nursing home care receive nothing. Perhaps a fairer system would be that all Americans are insured publicly for long-term care and that a far higher rate of inheritance taxes be imposed to finance public long-term care insurance. Such a system would tend to equalize the amount of money inherited by younger generations while protecting the savings of the elderly.

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Saccharin Revisited

To the Editor: The letter by Howard H. Frankel, MD, PhD, in the August 1993 issue on the "Resurgence of Saccharin"[1] suggests that Dr Frankel may be unaware of the research on saccharin conducted during the past 15 years and its current regulatory status. Studies of sodium saccharin conducted before 1977 showed that the addition of higher concentrations of this sweetener to the diet of rats was associated with bladder tumors. As a result, saccharin was banned in Canada and a proposal to ban saccharin was put forth by the United States Food and Drug

Administration. The latter was blocked by a congressional moratorium.

Of more than 20 epidemiologic studies of saccharin reported, only one, a case-control study,[2] reported an increased risk of bladder cancer. A subsequent and larger study by the same group[3] failed to confirm this finding. After an extensive review, the International Agency for Research on Cancer concluded that "The epidemiology data provide no clear evidence that saccharin alone, or in combination with cyclamates, causes urinary bladder cancer,"[4(p156)] and "There is no consistent evidence that the risk of cancer is increased among users of saccharin."[5(p224)]

Research on the mechanism underlying the development of bladder tumors in rats fed sodium saccharin has shown that the critical factors that lead to preneoplastic and neoplastic changes in the bladder are elevated urinary pH and sodium concentration. It has also been shown that bladder tumors do not occur when acid saccharin is fed to a rat or when sodium saccharin is fed together with the urinary acidifying agent, ammonium chloride, although the levels of saccharin anion in the urine in these animals are equivalent to or higher than those present when sodium saccharin alone is fed.[6] Bladder tumors occur in a rat fed high levels of sodium saccharin; they do not occur in the mouse, hamster, or monkey.[7] Bladder tumors also occur in rats fed similar high levels of the sodium salts of other organic acids, including sodium ascorbate, citrate, erythrobate, bicarbonate, aspartate, and glutamate.[8] The safety of these simple organic compounds has not been questioned. The published findings show that the development of bladder tumors associated with high dietary levels of the sodium salts of organic acids is a phenomenon that is unique to the rat and secondary to pronounced physiologic changes in the urine that occur in this species.

The extensive research on saccharin recently led the Health Protection Branch in Canada to conclude that "The majority view of toxicologists is that saccharin at low doses does not pose a health risk for humans" and to lift the ban on the use of saccharin in drugs and cosmetics (Health Protection Branch, Health and Welfare Canada, *Information Letter No. 800*, December 5, 1991). A petition for a recision of the ban on the use of saccharin in foods and beverages in Canada is pending. The Joint FAO-World Health Organization Expert Committee on Food Additives has increased the acceptable daily intake of saccharin from a temporary 0 to 2.5 to a permanent 0 to 5.0 mg per kg of body weight. The British Ministry of Agriculture, Fisheries, and Food has increased the acceptable daily intake for saccharin to 5 mg per kg of body weight, and in the United States the Food and Drug Administration has withdrawn its proposal to ban saccharin. The low levels of saccharin intake when this sweetener is used in pharmaceuticals, cosmetics, toothpastes, and the like represent only a small fraction of the daily intakes now considered safe for humans.

Research on saccharin has not only clearly established the safety of sodium saccharin for humans but as well has made a major contribution to our understanding of nongenotoxic carcinogens and their risk assessment. The saccharin saga once again illustrates the point made by Bernard Oser in 1981—"Man is not a big rat."[9]

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* * *

Dr Frankel Responds

To the Editor: Dr Chappel has presented an extensive literature review on the confusing experimental and legislative status of saccharin. His comments again illustrate the controversy that saccharin use still generates.

Although Chappel correctly reported that the US Food and Drug Administration (FDA) did withdraw the saccharin ban, he failed to point out that the FDA did not address the issue concerning the safety of saccharin and its salts. In addition, the FDA's withdrawal decision stipulated that it did not "preclude the agency from reproposing a ban or other restrictions on the use of saccharin and its salts at a later date. . . ."[1(p67442)]

The "Resurgence of Saccharin"[2] was not written to review the status of saccharin, but rather to question the scientific and common-sense rationale of introducing this controversial substance into newly formulated medicinal preparations when other thoroughly tested artificial sweeteners or sugar could have been used.

The following are indisputable facts:

- Reproducible dietary experiments have shown increased incidences of lymphoma and leukemia and transitional cell carcinoma of the urinary bladder in rats. In one study, saccharin induced papillary adenocarcinomas of the thyroid in mice.[3]
- The US Department of Health and Human Services officially lists saccharin as a substance that "may reasonably be anticipated to be a carcinogen."[3(pvii)]
- Although a study group from the International Agency for Research on Cancer has reported[4] that there is no adequate evidence for the carcinogenicity of saccharin in humans, some epidemiologic counterevidence does exist. Data presented have demonstrated an elevated trend in risk for both males and females.[5,6]

• In multigeneration studies using rats, administration of saccharin in the diet induced transitional cell carcinomas and papillomas of the urinary bladder in the first-generation male offspring.[3]

• Although saccharin has been added as a sweetener to newly formulated pediatric preparations of acetaminophen, cold and cough remedies, antidiarrheal medications, and other products, there is a scarcity of neonatal and infant studies. Most experimental and epidemiologic studies have focused on adult animal and human subjects.

• Medical research using rats and mice over the past 60 plus years has saved hundreds of thousands of human lives. To say, as Dr Chappel quotes, that the use of rats in research is invalid because "Man is not a big rat" is ludicrous.

• Recently, many pharmaceutical companies have marketed a plethora of new over-the-counter medications that contain saccharin, sugar (glucose, fructose, sucrose, confectioners' sugar, or dextrose), sorbitol, or all of these. This is both inappropriate and unnecessary. It makes no scientific sense.

It is the role of the government regulatory agencies to keep the public informed that saccharin has been added to these formulations. They have failed.

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Using the FAX

To the Editor: Use of facsimile (FAX) machines in the emergency department for transferring patient information is now well established. We report a case of international FAX transfer of patient data that affected the care of the patient.

Report of a Case

The patient, a 68-year-old woman, was visiting Yosemite National Park (California) on holiday from New Zealand when malaise, fatigue, sweats, and nausea developed. She had no chest pain or fever. Because of a history of two-vessel coronary artery bypass grafting four years before, the patient was extremely concerned about the possibility of heart disease.

The patient's blood pressure was 206/100 mm of mercury; her vital signs and cardiopulmonary and gastrointestinal examination findings were normal. A cardiogram showed depressed ST segments and inverted T waves inferolaterally without ectopy.

Because of the abnormal findings, we called the patient's hospital in Auckland. A FAX of a cardiogram done three years before was sent from New Zealand to Yosemite within minutes. This electrocardiogram showed that the inferolateral changes were new, adding to the database on the patient. The patient was treated and then transferred to a hospital two hours away for further care.

Discussion

Many uses for FAX machines in medical settings have been proposed.[1,2] In Yosemite we have routinely used this means to send or receive written consent for the release of records, for medical reports, or for cardiograms done within the United States. This was our first use of the technology to receive patient clinical data from overseas that affected decisions in the emergency setting.

We anticipate and encourage increased international use of FAX capabilities to improve the care of traveling patients who experience unexpected illness.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

The Gift

KAY F. McFARLAND, MD, *Columbia, South Carolina*

On Saturday mornings we do not have a formal morning report. We meet in the cafeteria and briefly review the new admissions before making rounds. There had been three admissions Friday night: a patient with chest pain, another with alcohol withdrawal seizures, and Johnny.

After we discussed the first two patients, the intern sighed and asked, "Do you know about Johnny?"

Wondering about his sudden change in mood, I replied, "No, tell us about him."

The intern seemed on edge, perhaps tired from being up all night. "Johnny is a 31-year-old man who has been admitted many times for complications of epidermolysis bullosa. Now the problem is different. A few hours before admission, he lost the use of his right arm. Rather than my presenting the physical findings, maybe you should just see him. He looks like 'E.T.' "

As we left the cafeteria and took the elevator to the seventh floor, I realized that we were all tense, knowing Johnny's rare, inherited skin condition was not curable. When our entourage of 2 interns, a resident, 2 third-year medical students, a fourth-year student, and I entered his room, I was wondering how we could help this patient.

When I saw Johnny, I gasped. He looked like a living mummy. His broomstick-sized extremities were wrapped in gauze to the trunk. He had no hair. His head appeared too large for his body, and his eyes were widely set. He did look like "E.T."

His eyes, penetrating and pleading, fixed on me. He spoke in a high-pitched, squeaky voice, "Please fix me. Fix my arm. I need my arm to eat. Won't you fix it?" Before I had a chance to answer, he pleaded again, "Make my arm work. I need it."

My first instinct was to touch him, but there was the gauze wrapped all around his arms. He had no hands. I did not know exactly what to do, and yet I felt increasing pressure hearing the house staff and students moving restlessly behind me. I was a little afraid to touch him for fear that his skin would peel off like tissue paper. Then I noticed that his chest was not wrapped with gauze, so I examined his heart and lungs.

I felt an overwhelming sense of helplessness that intensified when he pleaded again. "I need both arms to eat. Fix my arm so I can eat."

He did not have a hand to hold a spoon and needed both stubs to feed himself. He tried to demonstrate, but he could not move his left arm enough to even touch his right. I heard a couple of nervous coughs from the house staff.

Johnny continued, "There are two things that I like to do—watch TV and eat. Now I can't eat by myself. You will fix my arm?" His eyes pleaded as much as his words.

With a confidence that I really did not feel, I replied, "Johnny, we'll find a way for you to feed yourself."

As we left the room, I could believe that he weighed only 60 pounds. He looked like wrapped-up bones. In the hall outside his room, none of us said anything for a few minutes, until we could switch back to thinking scientifically. Then we figured out the details of his management: How many units of blood does he need? Should we do a computed tomographic scan of his head because of the stroke? Most important, what could we devise so he can feed himself with his right arm?

For days after that, I could not get Johnny out of my mind. I wondered how his mother, who had been there during rounds that first day, had been able to take care of him for 31 years. He had needed total care. She had seen him grow up and never walk. Even worse, what must it have been like for her not to be able to touch him for fear of leaving a permanent mark on his delicate skin? How had they both kept their ability to be positive in what seemed to be a hopeless situation? How could he still believe that we would help him when he had gone through so much already?

My answer came when we gave him a spoon that had a long handle with a hook that just fit around his right arm. His excitement was like a child's on Christmas Day. His eyes sparkled; ours filled with tears. Perhaps he will never know that he gave us much more than we could give him.

(McFarland KF: The gift. West J Med 1994; 160:586)

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Hot Apple Pie for Emma

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I first met Emma a year ago, when she presented with increasing angina. As a cardiovascular surgeon, I was asked to consult with this 78-year-old woman with a long-standing history of diabetes mellitus and severe peripheral vascular disease. She had had coronary bypass surgery more than ten years previously and, in the interim, had undergone an above-the-knee amputation for lower extremity ischemia.

Angiography showed only one coronary vessel suitable for bypass grafting. Because of her associated conditions and the substantial risk of reoperation, she was reluctant to undergo a surgical procedure. We decided instead to make sure her medical treatment was optimal. This insightful lady understood her disease well, was very compliant, and was under the care of a thoughtful cardiologist in whom she had the utmost confidence.

She did well until this spring, when she was readmitted to hospital with progressive cardiac failure and angina. She was grateful for the care that had permitted her to remain out of the hospital for almost nine months: "Dr Lee has done everything to keep this old machine going."

I again assessed her condition, and together we decided not to operate because of the inordinate risks. Almost daily I would stop by, if only to greet her. This joyful, intelligent lady always had a wise word for me. On one visit, I asked if there was anything I could do for her or anything she desired. She looked at me with her probing eyes and said, "You know, I really would like a piece of apple pie—hot apple pie." When I suggested adding a piece of cheese or a scoop of ice cream, she chided me, saying, "Now, Doctor, you know better than that!" I promised to deliver.

Days went by and apple pie was not to be found in the cafeteria. One Saturday morning, I crossed paths with Marguerite, a food service employee known for her friendliness and numerous acts of kindness on behalf of the patients. I presented her with my problem, and she promised to take care of it.

The next day, I made my usual visit and was happy to learn that Emma had received the hot apple pie with her dinner tray the evening before and had enjoyed it very much. The following week, I offered to repeat the treat, but she declined. By week's end, she was in the intensive care unit with progressive cardiac failure. I visited her one evening and found her too weak to talk except to tell me she was tired and just wanted to rest. She died the next morning.

Patients are not always suitable candidates for our sophisticated treatments, and we not infrequently arrive at an impasse. Sometimes an encouraging word—or even a piece of apple pie—is the best we can do.

Many incursions on our practice can distract us from providing the best care for our patients. I hope, though, that we will always be able to treat patients in a very personal way and that when a seemingly unimportant request is made that will offer some degree of comfort, we will be able to deliver.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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STEPHEN J. McPHEE, MD
Assistant Editors

(Tucker BL: Hot apple pie for Emma. West J Med 1994; 160:587)

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The original manuscript and two copies should be submitted on standard-sized heavy bond paper. Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides. Manuscripts transmitted by facsimile machine are not acceptable unless requested by the Editors.

All values should be in Système International (SI) units, with metric equivalents following in parentheses. Temperature readings should be given in Celsius. Use the generic name of drugs, with the salt or ester given when first used.

Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints, with the figure number, author's name, and top of the photo indicated with a label on the back. Patients (and relatives) have a right to anonymity in published clinical documentation. Details that might identify patients should be avoided unless essential for scientific purposes. Masking of the eye region in photographs of patients may be inadequate protection of anonymity. If identification of patients is unavoidable, informed consent should be obtained, and this should be clearly stated in the article. Changing data on patients should not be used as a way of securing anonymity. Figure legends, to be typed in sequence on the same page, should be in complete sentences. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

Reprints

A form to order reprints will be sent to the author when the article is published.

References

All references should be cited in the text using superscript numbers and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in *WJM* style (see previous copy of journal).

All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.

For a complete guide to WJM *style for references, see the two-page Instructions for Authors in a previous issue.*

CHECKLIST

- Original manuscript and 2 copies
- **Everything** including tables and references double-spaced
- Illustrations, black and white glossy, identified with lead author's name—3 sets, plus figure legends that describe fully and in complete sentences what the figure depicts
- Letter of transmittal that includes release of copyright, statement of conflict of interest, and authorship responsibility, **signed by all authors**
- A 200-word abstract
- Title page that includes current affiliation of all authors and address **and telephone number** for corresponding author
- Permission-to-borrow letters for any previously published illustrations or tables
- All references numbered consecutively, double-spaced, in *WJM* style, and cited in text. No unpublished data or nonscientific publications listed in references (include in text)

(Continued from Page 523)

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

September 21-24—**Utah Medical Association—Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: Utah Medical Association.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 17—**Interventional Radiology.** Seattle. Fri. Contact: U/W.

June 18-19—**Pediatric Advanced Life Support.** Seattle. Sat-Sun. Contact: Children's, (206) 368-4802.

June 27-28—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS CME.

July 29-30—**From Bench to Bedside: A State of the Art HIV Conference for Primary Care Providers.** Seattle. Fri-Sat. Contact: U/W.

August 4-6—**Breast Cancer in Young Women.** Seattle. Thurs-Sat. Contact: U/W.

August 8-13—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Sat. Contact: U/W.

September 9—**Interventional Radiology.** Seattle. Fri. Contact: U/W.

September 9-11—**Radiation Health Effects and Hanford: A Joint Conference for Concerned Citizens and Health Care Providers.** Spokane. Fri-Sun. Contact: U/W.

September 10-11—**Pediatric Advanced Life Support.** Seattle. Sat-Sun. Contact: Children's, (206) 368-4802.

September 11-16—**North Pacific Pediatric Society—149th Meeting.** Blaine. Sun-Fri. Contact: Norma Brooks, (206) 248-2229.

September 19-23—**Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 29-30—**New Approaches to Common Urinary Tract Problems in Children.** Seattle. Thurs-Fri. Contact: Children's, (206) 526-2501.

October 27-30—**7th Annual Pediatric Critical Care Colloquium.** Seattle. Thurs-Sun. Contact: Children's, (206) 526-2501.

October 28-29—**Mental Health Update.** Seattle. Fri-Sat. Contact: U/W.

November 3-4—**Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 4—**Muscular Dystrophy and Related Disorders.** Seattle. Fri. Contact: Children's, (206) 526-2501.

November 11-12—**Pediatric Advanced Life Support.** Seattle. Fri-Sat. Contact: Children's, (206) 368-4802.

December 2—**Pediatric Update.** Seattle. Fri. Contact: Children's, (206) 526-2501.

December 8-10—**10th Annual Infectious Disease Conference.** Seattle. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 261-2160.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762. ◆

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Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call (800) 873-0786.**

REWARDING OPPORTUNITY to practice the full range of Family Medicine (with Obstetrical option if desired) in a long-standing community health center. BC/BE Family Practitioners needed to join existing staff composed of Family Physicians, Internists, and Pediatricians on the Waianae Coast. Academic positions also available. Full benefits package and competitive salary. If interested, call or send CV to Pua Kalawa, Waianae Coast Comprehensive Health Center, 86-260 Farrington Highway, Waianae, HI 96792; (808) 696-7081.

FAMILY PRACTICE. SALEM, OREGON. 20 plus multispecialty group in Oregon's beautiful Willamette Valley seeks BC/BE Family Practice physician. No OB. Good call rotation. Salary plus incentive, outstanding benefits. 45 minutes from Portland. Savor city life without the headaches. Natural wonders and recreational amenities abound. Contact Yvonne Carscadden at (503) 399-2470 or send CV to Salem Clinic, 2020 Capitol NE, Salem, OR 97303.

RAPIDLY GROWING, NEWLY FORMED multispecialty group seeking a BC/BE Family Physician with California license. Guaranteed salary with many incentives, benefits, and all expenses paid. Beautiful valley, great schools, affordable housing and many recreational opportunities. Submit résumé to Hemacinto Medical Group, 2390 E Florida Ave, #101, Hemet, CA 92544, or call (909) 652-2252.

INTERNIST/FAMILY PRACTICE. Positions for well loved multidisciplinary Geriatric health center. Part of east San Francisco bay area community clinic network. Participation in hospital and call coverage desired. Resident teaching and UCSF affiliation possible. Call (510) 644-6060.

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Physician needed for busy, Urgent Care/Industrial Medicine, walk-in clinics. Flexible hours, generous benefits, excellent salary. Excellent locations in exciting Las Vegas/Laughlin area offer numerous recreational activities and the finest entertainment. CV to:

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(702) 731-1278

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CONTACT with CV to: **Nancy Chaffins**

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(509) 482-2133
FAX: (509) 482-2187

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BC/BE FAMILY PRACTICE opportunity 2 1/2 hours north of Sacramento. Eligible loan repayment site. NO CALL. NO OB.

FAX CV or call collect to
Joyce Marks, Marks Medical Placements
(310) 556-2126, FAX (310) 556-1604

NORTHERN CALIFORNIA RECREATION AREA. Multispecialty group has immediate opening for an Internal Medicine practitioner with a particular interest in Critical Care. Clinical activities involve full range of Internal Medicine outpatient and inpatient practice. Beautiful northern California location offers abundant recreational opportunities as well as small town living. Competitive salary and comprehensive benefit package. Please send CV to 10978 Donner Pass Rd, Truckee, CA 96161.

POSITIONS AVAILABLE FOR BC/BE Internists, Family Practitioners, and Pediatricians at UC Davis Medical Group in Sacramento and Davis. Physicians will have volunteer clinical faculty appointment with UC Davis School of Medicine. Starting salary ($80,000-$110,000). Send CV to Denyse Nishio, MD, 2825 J St, Ste 400, Sacramento, CA 95816. UC Davis is an EOE employer.

ENDOCRINOLOGIST OR INTERNIST WANTED to gradually take over large practice in San Francisco bay area. FAX inquiry to (415) 697-1043.

(Continued on Page 599)

CHALLENGING OPPORTUNITY FOR A PUBLIC HEALTH LEADER

HCA Division Manager II, Medical

$77,484 - $116,568/Year

The **County of Orange Health Care Agency** has an excellent opportunity for leadership as the Division Manager for Disease Prevention and Control. This individual will be responsible for providing direction and coordination to Disease Control (TB & STD control, HIV activities), Epidemiology (Births & Deaths Registration, Field Epidemiology), Public Health Laboratory and Health Promotion and Disease Prevention (Multi-Ethnic Health Services, Employee Health, Tobacco Use Prevention, Injury Prevention).

Requires a CA Physician's license and four years of physician experience, including one year in an administrative capacity. Call **Lori Navarrete** at **(714) 834-6119** for information and application materials. Resumes cannot be accepted.

APPLY IMMEDIATELY! HCA Human Resources Department, 511 North Sycamore Street, Santa Ana, CA 92701

County of Orange

Affirmative Action Empl M/F

(Continued from Page 598)

PHYSICIANS WANTED

ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

FAMILY PRACTICE BC/BE needed for community health center, San Diego. Contact J. Browne, (619) 234-8171.

BC OR RECENTLY BE PHYSICIANS NEEDED. Los Angeles and Seattle metropolitan areas: Family Practice, Pediatrics, OB/GYN, Industrial Medicine, Urgent Care, and Internal Medicine. Northern Arizona: Invasive/Noninvasive Cardiologists and Internal Medicine. Call Chris Warner, Panther Enterprises Physician Recruiting and Placement, (800) 235-7601.

(Continued on Page 600)

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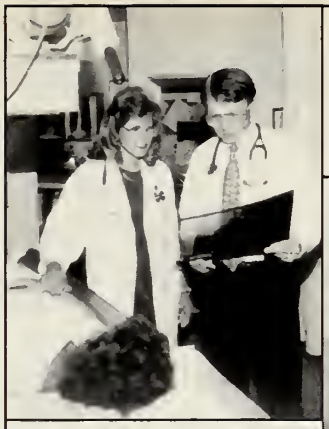

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As part of our team, you'll enjoy a predictable schedule. What's more, CIGNA HealthCare offers competitive salaries, comprehensive benefits, and the resources of a healthcare leader. For more information, call or send your CV to:

California: CIGNA Medical Group, Physician Recruitment, 505 N. Brand Blvd., Suite 400-49, Glendale, CA 91203, (800) 468-9013.

Arizona: CIGNA HealthCare of AZ, Physician Recruitment, 11001 N. Black Canyon Hwy., Suite 401-49, Phoenix, AZ 85029, (800) 252-2471.

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Come Enjoy a Quality Lifestyle!

SPOKANE, WASHINGTON - this unique city offers you affordable housing, excellent schools and universities, a regional arts and cultural center, and unlimited recreational opportunities in this mild four season climate.

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ROCKWOOD CLINIC, P.S., a physician directed multi-specialty medical group practice offering both primary and tertiary services at six Spokane area locations seeks board certified primary care physicians for a new satellite clinic located in a rapidly growing suburban area.

Come practice with an established group providing you the environment to: Maintain your autonomy, concentrate on patient care, be relieved from business hassles, have strong collegial support and a favorable call schedule. Substantial benefits package includes: a competitive salary leading to early share holder status, six weeks vacation and paid CME.
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Rockwood Clinic P.S.
E. 400 5th Ave., P.O. Box 3649
Spokane, WA 99220-3649
Phone (509) 838-2531
Fax (509) 455-5315

ROCKWOOD CLINIC, P.S. ®

(Continued from Page 599)

PHYSICIANS WANTED

THE SOUTHWEST IS CALLING

Leading medical providers in Arizona, Nevada, Utah, Colorado, and New Mexico have asked us to find the best available BC/BE physicians in the specialties of Orthopedic Surgery, Internal Medicine, Family Practice, Pediatrics, Urgent Care, OB/GYN, Psychiatry, Hematology/Oncology, Radiology, Occupational Medicine, MED/PED, Cardiology, Nephrology, and Pulmonology. Top benefits, profit sharing, guarantee first two years, plus incentive pay, early shareholder. Please call CPR Tucson, (800) 658-9166, FAX (602) 322-2676, or in Phoenix, (800) 657-0354, FAX (602) 433-9548.

WESTERN MONTANA. Busy three physician Internal Medicine group seeks fourth General Internist. Superb opportunity with rapid growth potential for BC/BE Generalist. Position particularly attractive for those with ICU interest. Outstanding recreational opportunities abound. Salary guarantee and excellent benefits provided. Send CV to Keith Popovich, MD, Western Montana Clinic Butte, 300 W Mercury, Butte, MT 59701.

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PHYSICIANS WANTED

ELKO REGIONAL MEDICAL CENTER
NEVADA'S OLDEST MULTISPECIALTY CLINIC

is currently seeking an OB/GYN, two Family Practice Physicians, a Pediatrician, and an Orthopedic Surgeon. Elko is a growing, beautiful rural area. It has a booming economy with a flourishing practice opportunity. Six month salary guarantee leading to a full partnership. Great benefit package.

Please contact Jane Descutner
762 14th St, Elko, NV 89801
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PACIFIC NORTHWEST AND ROCKY MOUNTAIN/SOUTHWEST LOCATIONS. Locum tenens assignments in Emergency Medicine, Primary Care, and Radiology. Urgent need for locum tenens. Benefits include malpractice, lodging, and transportation. Assignments vary in duration. Permanent placement also available. Call or write Lorie or Susan, Interim Physicians, 4155 E Jewell, #1018, Denver, CO 80222; (800) 669-0718.

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MEDICAL SUPERVISOR

Become part of our management team at Miles Inc Stockton Plasma Center.

We are looking for a Physician to perform medical history and physical examinations, assess screening and laboratory test results.

As part of our management team you will participate in employee safety, education, and training programs.

Qualified applicants need MD, California license, and certified in CPR.

If you are interested in Monday through Friday, full-time days, and excellent benefits (including):

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- DENTAL
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- LICENSING FEES

Contact:
NORM GRAY

MILES

(209) 465-0284

NORTHERN CALIFORNIA—BC/BE GENERAL INTERNIST sought to join progressive prepaid multispecialty group practice at the Kaiser Permanente Medical Center in Santa Rosa. Department of Medicine includes 13 generalists and 10 specialists; call schedule is reasonable. Spanish fluency preferred. Free-standing medical clinic since 1980; 106-bed hospital on same campus since 1990. Located on the northern edge of the San Francisco bay area, Santa Rosa offers a rural/suburban lifestyle with easy access to the amenities of a major metropolitan area. Competitive salary, generous benefits and comprehensive benefit package. For more information, send CV and cover letter to Gordon Leung, The Permanente Medical Group, Inc, Physician Recruitment Services, Dept 64, 1814 Franklin, 4th Floor, Oakland, CA 94612. EOE.

CLASSIFIED DEADLINES:

Issue	Due Date
Aug:	July 1
Sept:	Aug 1
Oct:	Sept 1

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PHYSICIANS WANTED

PRIMARY CARE

OREGON & S.W. WASHINGTON

Northwest Permanente, P.C., a professional group of physicians providing medical services to 380,000 members of Kaiser Permanente in Oregon and SW Washington, has full-time and part-time opportunities in general family practice or urgent care for BC/BE Family Physicians and Internists in the Portland/Vancouver and Salem, OR areas and Longview, WA. In Salem, opportunities exist for Family Physicians or Internists with a special interest or expertise in geriatrics.

Our program offers a professionally stimulating environment, a quality lifestyle in the Pacific Northwest, signing bonus and a competitive salary/benefits package. Forward inquiry and C.V. to: W. J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., #300, Portland, OR 97210-5398. EOE.

KAISER PERMANENTE
Northwest Permanente P.C.
Physicians and Surgeons

PHYSICIANS

The California Department of Corrections with 30 locations statewide has a number of opportunities available for Physicians and Psychiatrists.

Internal Medicine • General Practice • Family Practice
(Two Facilities in Blythe)
Ironwood State Prison and Chuckawalla Valley State Prison
Riverside County - Southern California

California Correctional Center in Susanville
Centinela State Prison in El Centro

OTHER OPENINGS EXIST AT: Calipatria, Wasco, Pelican Bay, Vacaville, Madera, Lancaster, Norco, Tehachapi, Corcoran, San Quentin, Solano, Soledad and Delano.

HIV Physicians
California Medical Facility at Vacaville

Chief Medical Officer Opportunities also exist at several locations.
Two Medical Consultants for Southern California and the Central Valley area for Health Care Services Division headquartered in Sacramento.

PSYCHIATRISTS

New Prison to open October 1994
Pleasant Valley State Prison in Coalinga, Central California

Staff Psychiatrists
Vacaville, San Luis Obispo, Chino, Soledad/Monterey, Madera, Corcoran, Crescent City, Lancaster, Delano, Ione, Wasco, Calipatria and Solano.

Senior Psychiatrist
Tehachapi

GOOD NEWS!! New legislation allows for Safety Retirement Package. Call for additional information.

Contact: Medical Recruiter
(916) 327-7081. Send or fax CV to:
California Department of Corrections
Dept. DHCS, P.O. Box 942883, Sacramento, CA 94283-0001. Fax (916) 327-1804 EOE.

WYOMING INTERNIST NEEDED. BC/BE Internist to join established Internist in beautiful western Wyoming. Join a progressive medical staff in a growing small city of 13,000 (service area approximately 24,000). Outdoor recreational opportunities are outstanding with world-class skiing and a major metropolitan area within one hour. Contact Rob Allen, IHC-Evanston Regional Hospital, 190 Arrowhead Dr, Evanston, WY 82930, or call (307) 789-3636.

BOISE, IDAHO. IDAHO EMERGENCY PHYSICIANS is in the process of expanding our organization. We have two Urgent Care centers with plans to add an additional three centers over the next few months. We have full-time and part-time opportunities for experienced Primary Emergency Medicine physicians. Mid-level practitioners considered. Positions are salaried with superb benefits. Ownership potential. Ideal work week with flexibility. Extensive administrative support. Send résumé or CV for our return package. Recruiting Chairman, IEP, 2312 N Cole Rd, Ste B, Boise, ID 83704.

BC/BE FAMILY PRACTITIONER with interest in OB and a commitment to caring for the underserved needed to join clinics in Grandview and Walla Walla, Washington, and Hermiston, Oregon. All clinics located in rural settings with abundant recreational activities. Competitive salary, Public Health Service loan repayment slots, and excellent benefit package including paid malpractice. Contact Mayling Chin, Recruiting Specialist, or Ann Garza, Director of Personnel at Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948, or (509) 865-5898.

PHYSICIANS WANTED

THE VA MEDICAL CENTER, PRESCOTT, ARIZONA

is seeking a BC/BE Internist or Family Practice Physician. Regular hours. Experience with Holter monitors, treadmill testing, and/or endoscopy desirable but not necessary. Prescott is a lovely area with beautiful surroundings, clean air, pleasant lifestyle, wonderful dry four season climate. Interested physicians may call (602) 445-4860, ext 6640, or send CV to Chief, Medical Service, VA Medical Center, Prescott, AZ 86313.

EOE

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FAMILY PRACTICE/CHEMICAL DEPENDENCY/San Francisco bay area. BC/BE Family Physician needed with some chemical dependency experience interested in all phases of Family Medicine which would include Intensive Care Medicine, interest in chemical dependency detox units, chemical dependency consultations in the various hospital wards, MRO-type activities, Industrial Medicine. Office based Family Practice and surgical abilities also preferred. Salary guaranteed and negotiable. Join credentialed, excellently rated practice that's in the East San Francisco bay area. Call (510) 680-8955.

(Continued on Page 602)

DIRECTOR OF MEDICAL AFFAIRS

VALLEY MEDICAL CENTER is a progressive 417 licensed be teaching, tertiary care hospital, including a Level I Trauma Center and Burn Center, affiliated with the University of California, San Francisco School of Medicine. The organization is seeking a qualified physician to direct its Department of Medical Affairs. Under the direction of the Hospital Administration, the Director of Medical Affairs is responsible for the educational activities conducted at Valley medical Center in collaboration with UCSF and the Faculty Medical Group. The educational activities include clinical clerkships for UCSF undergraduate medical students, 10 residency programs, with over 160 residents, as well as continuing medical educational programs.

This individual will be a member of the senior management team and will participate in the long-range planning, operational, and budgetary direction of the organization. This individual will also actively participate in medical staff and quality improvement activities, as well as other program affiliations.

Prospective candidates should have extensive experience in academic medicine, faculty practice planning, as well as experience and knowledge of clinical teaching activities, and the development of medical education programs. Graduation from an accredited college or university with a Doctor of Medicine Degree that is acceptable within the United States' accredited college or university system is required. This individual must be eligible for and obtain a valid license as a Physician and Surgeon issued by the State of California, Department of Consumer Affairs, Medical Board of California, and must also be eligible for and obtain an academic appointment from the University of California, San Francisco School of Medicine.

Please submit CV and/or direct all inquiries to:

Valley Medical Center
Administrative Office
445 South Cedar Avenue
Fresno, CA 93702
(209) 453-5060, FAX: (209) 453-1787

(Continued from Page 601)

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(Continued on Page 603)

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Heidi Thomas
Physician Resources Coordinator
San Jose Medical Group
45 S 17th St, San Jose, CA 95112;
(408) 282-7833, FAX (408) 297-0939

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FRIENDLY PEOPLE-FAMILY MEDICINE

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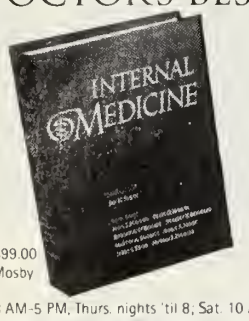

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Arizona Medical Association, Inc–810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 2-4, 1994, Scottsdale Plaza Resort.

California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-7, 1995, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 7-11, 1994, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 7-9, 1994, Ritz-Carlton Maunalani, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 28-30, 1994, Sun Valley.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1994, Holiday Inn, Great Falls.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1995, date and location to be announced.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1995, date and location to be announced.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-24, 1994, University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 22-24, 1994, Wenatchee.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 9-11, 1994, Jackson Lake Lodge, Moran.

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

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Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased in therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t1/2) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS: Skeletal Muscle.

Antipyrine. Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine. The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* [1 hour prior to PRAVACHOL (pravastatin sodium)], *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs. During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK + / − mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter^2). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General**.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions. An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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AVAILABLE ON MEDI-CAL

Effective lipid management doesn't have to be tough

- Improves key lipids — significant reduction in LDL-C[1]
- Excellent safety profile
- Easy for patients — once-daily dosing, well tolerated
- Usual dose: 20 mg once daily at bedtime, with or without food

PRAVACHOL®

pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

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